IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ROQUETTE FRÈRES,	)	
	)	
Plaintiff,	)	
	)	
v.	)	C.A. No. 06-540 (***)
	)	
SPI PHARMA, INC. and DRYTEC LTD.,	)	
	)	
Defendants.	)	

PLAINTIFF'S ANSWERING BRIEF IN OPPOSITION TO DEFENDANT'S MOTION FOR LEAVE TO AMEND ITS ANSWER, DEFENSES AND COUNTERCLAIMS

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NATURE AND STAGE OF THE PROCEEDINGS

Roquette Frères ("Roquette") filed its First Amended Complaint against SPI Pharma, Inc. ("SPI") on October 20, 2006, alleging that SPI infringed Roquette's U.S. Patent No. 5,573,777 ("the '777 patent"). (D.I. 9). SPI answered on November 6, 2006. (D.I. 15). In its Answer, SPI presented counterclaims and affirmative defenses that included invalidity, laches and equitable estoppel but excluded any counterclaim, affirmative defense or allegation related to inequitable conduct.

On December 28, 2007, more than a year after filing its Answer and more than seven months after the deadline to amend or supplement pleadings in this case, SPI requested leave to amend its pleadings to add entirely new and distinct theories of inequitable conduct.

Because SPI's representations made in support of its new theories of inequitable conduct are demonstrably inaccurate and misleading, SPI's motion should be denied as futile and/or made in bad faith. Separately, SPI's lengthy delay in seeking to amend its Answer, without reasonable explanation or requisite showing of good cause, would unduly prejudice Roquette and SPI's motion should be denied for that reason.

STATEMENT OF FACTS

SPI in both its proposed First Amended Answer (D.I. 147, exhibit A) and accompanying brief (D.I. 148, hereafter "SPI Br.") represents that (i) the specification of the '777 patent mischaracterizes or conceals material prior art and (ii) the inventors confirmed that allegation during their depositions. On both counts, SPI's representations are inaccurate and misleading, and for those reasons are futile and apparently made in bad faith.

I. THE '777 PATENT ACCURATELY CHARACTERIZES, AND SPI MISCHARACTERIZES, WHAT IS DISCLOSED IN JP 61-85331

SPI contends at page 2 of its brief that the '777 patent specification incorrectly characterizes Japanese Patent Application 61-85331 ("JP 61-85331") as disclosing only products that contain an excessively high content of particles smaller than 75 microns. According to SPI, the samples disclosed in JP 61-85331 contain only 4-6% particles of that size. (SPI Br. at p. 2). In these assertions, SPI provides an incomplete presentation of what the '777 patent states and misrepresents what JP 61-85331 discloses, which together would mislead the Court to infer a patently incorrect conclusion.

SPI presents in its brief only a selected portion of what the '777 patent states regarding JP 61-85331, specifically, that "It emerges from this document that, with less than 5% starch hydrolysate, the excipient obtained according to this process, . . . always has an excessively high content of particles with a size of less than 200 mesh (75 microns)." (SPI Br. at p. 2). SPI omits from its brief the very next two sentences of the '777 patent, which continue,

> This value, in the region of 70%, is lowered when the starch hydrolysate represents 15% and 25% of the excipient, but the latter then unfortunately becomes excessively hygroscopic and cariogenic and no longer corresponds to the definitions of the Pharmacopoeiae in force. In other words, this document does not teach the means of preparing a pulverulent mannitol containing few fine particles and which, moreover, is non-hygroscopic and non-cariogenic. ('777 Patent, Exh. A to SPI Br., at Col. 3, ll. 30-39) (emphasis added).

Thus, when read without SPI's selected omission, the '777 patent clearly states that JP 61-85331 discloses mannitol products that have excessively high levels of particles smaller than 75 microns when starch hydrolysate is low (e.g., less than 5.0%) and have fewer particles of that size when starch hydrolysate is high (e.g., 15% and 25%) but these latter products incur other deficiencies, including excessive hygroscopicity.

SPI also misrepresents in its brief what JP 61-85331 discloses. According to SPI, "JP 61-85331 contains data that include, *inter alia*, particle size distribution percentages for four samples of the excipient obtained according to the method described therein" and that "[t]hese data show that the samples had only 4-6% of particles with a size of less than 200 mesh (75 microns) – not an 'excessively high content' as Applicants represented to the PTO in the '777 patent specification." (SPI Br. at p. 2).

JP 61-85331 discloses no such data. Rather, that document discloses data for four samples obtained according to that document's disclosed process, two of which include not more than 5.0% starch hydrolysate and yield in the region of 70% particles smaller than 75 microns, the other two of which include, respectively, 15% and 25% starch hydrolysate which lowers the amount of particles of that size but increases their hygroscopicity. In other words, JP 61-85331 discloses precisely what the '777 patent states, and precisely not what SPI states.

We attach as Exh. A hereto a copy and complete English translation of JP 61-85331.[1] At Table 1 (Exh. A at p. 6), that document provides particle size data for the four samples ("Embodiments 1-4"). Embodiments 1 and 2 include 5.0% or less starch hydrolysate [2] and exhibit respectively 89% and 73% particles having a diameter smaller than 200 mesh (i.e. 75 microns), which the '777 patent correctly represents. Embodiments 3 and 4 include respectively

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[1] It is noteworthy that SPI failed to substantiate its representations regarding JP 61-85331 by providing the Court with that document, an English translation, or even a citation to what SPI considers the document's relevant part.

[2] See Exh. A at p. 5, describing Embodiment 1 as being formed from 9.95 kg of mannitol and 25 kg of 0.2 w.w% hydrolyzed starch (0.2% X 25 kg = 0.05 kg hydrolyzed starch), which corresponds to 0.5% hydrolyzed starch, and describing Embodiment 2 as being formed from 9.5 kg of mannitol and 20 kg of 2.5 w.w% hydrolyzed starch (2.5% X 20 kg = 0.5 kg hydrolyzed starch), which corresponds to 5.0% hydrolyzed starch.

15% and 25% starch hydrolysate[3] and exhibit lower values – i.e., 4% and 9% respectively – of particles smaller than 75 microns, which the '777 patent also correctly represents.[4] Table 1 of Exh. A further indicates that Embodiments 3 and 4 were characterized by significantly greater hygroscopicity (0.81% and 1.36%) compared with Embodiments 1 and 2 (0.02% and 0.41%), e.g., a more than forty-fold increase comparing Embodiments 1 and 3, which the '777 patent also correctly represents.

Thus, SPI's assertion that JP 61-85331 discloses four samples having 4-6% particles less than 75 microns in size is demonstrably false, and its failure to inform the Court that the '777 patent in fact addresses and describes the two samples that did have fewer particles of that size is misleading.

The English translation submitted herewith in Exh. A confirms that JP 61-85331 discloses precisely what the '777 Patent represents – the product having low starch hydrolysate exhibited excessively high amounts of small particles (in the range of 70%) and the disclosed product having starch hydrolysate increased to 15% and 25% decreased the amount of small particles but significantly increased the hygroscopicity.

II. THE '777 PATENT ACCURATELY CHARACTERIZES, AND SPI MISCHARACTERIZES, WHAT IS DISCLOSED IN JP 61-85330

SPI correctly reproduces at p. 2 of its brief the '777 patent's statement regarding Japanese Patent Application 61-85330 ("JP 61-85330"), namely, that the products obtained under

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[3] See Exh. A at p. 5, describing Embodiment 3 as being formed from 8.5 kg of mannitol and 15 kg of 10.0 w.w% hydrolyzed starch (10.0% X 15 kg = 1.5 kg hydrolyzed starch), which corresponds to 15% hydrolyzed starch, and describing Embodiment 4 as being formed from 7.5 kg of mannitol and 25 kg of 10.0 w.w% hydrolyzed starch (10.0% X 25 kg = 2.5 kg hydrolyzed starch), which corresponds to 25% hydrolyzed starch.

[4] SPI's representation that the samples reported in JP 61-85331 had 4-6% particles smaller than 75 microns is incorrect even as to these two Embodiments, which further exemplifies SPI's apparent lack of attention in assessing and characterizing that document's disclosure.

that document contain "more than 50% of particles with a size of less than 200 mesh (75 microns)." SPI's next assertion, however, that JP 61-85330 includes data showing samples with only 7-8% particles of less than 75 microns (which SPI again presents to the Court without benefit of the document, English translation, or citation), does not exist in the Japanese document.

We attach as Exh. B hereto a copy and complete English translation of JP 61-85330. The only particle size data included in JP 61-85330 is provided in Table I. (See Exh. B at p. 7). Table I provides data for two samples obtained according to the method described ("Embodiment examples 1 and 2"). (See Exh. B at p. 6). For each sample, the amount of particles that were less than 75 microns in size is provided in the row labeled "Particle size (%) – 200 mesh through"). There, it is plainly reported that Embodiment examples 1 and 2, exhibited 74% and 56% particles smaller than 75 microns.[5] That data is consistent with the document's description that for each of Embodiment examples 1 and 2, "a fine powder was obtained." (Exh. B at p. 6) (emphasis added).

Consistent with the data reported in Table I of JP 61-85330, the '777 Patent accurately states that the products obtained under the conditions of that document contain "more than 50% of particles with a size of less than 200 mesh (75 microns)." ('777 Patent, Exh. A to SPI Br., at Col. 3, ll. 44-48).

Contrary to SPI's assertion, JP 61-85330 nowhere mentions any product having between 7-8% particles smaller than 75 microns.

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[5] Table I of JP 61-85330 also provides data for two comparative examples ("Referential examples 1 and 2"), which are obtained by other methods and for which Table I reports even higher amounts of particles smaller than 75 microns, specifically, 84% and 89%, respectively. (Exh. B at p. 7).

At best, SPI's mischaracterization of JP 61-85330 is careless error. In any light, it is patently false and misleading.

III. SPI'S ASSERTIONS REGARDING JP 55-36646 AND U.S. 3,145,146 ARE IMMATERIAL TO ANY CONTENTION OF INEQUITABLE CONDUCT

SPI complains at pages 3-4 of its brief that the '777 patent comments on the particle sizes that would be obtained under the process conditions described in Japanese Patent Application 55-36646 ("JP 55-36646") and U.S. Patent No. 3,145,146 ("the '146 patent") whereas those publications lack specific particle size data. SPI does not allege any inaccuracy or misrepresentation in the '777 patent's comments.

We attach as Exh. C hereto a copy and complete English translation of JP 55-36646. The '777 patent explains *inter alia* that the spray-drying process described in JP 55-36646 is only applied to sorbitol and xylitol. ('777 Patent, Exh. A to SPI Br., at Col. 3, ll. 49-65). That comment is accurate. (See Exh. C at pp. 5-6, "Embodiments 1-5"). The '777 patent further comments that although JP 55-36646 suggests that mannitol might be spray-dried under the same conditions, such a process yields mannitol product that "always contains a very high content of fine particles, like the product described in Japanese Patent Application JP 61-85330." ('777 Patent, Exh. A to SPI Br., at Col. 3, ll. 54-65). In light of the data for spray-dried mannitol provided in JP 61-85330 discussed *supra*, that comment also appears accurate.

Moreover, SPI does not allege that these comments made in the '777 patent are in any way inaccurate or misleading. Rather, SPI merely asserts that co-inventor Boonaert stated in his deposition that he did not personally verify the comment. (SPI Br. at p. 3). Roquette is aware of no requirement that each co-inventor personally verify every comment made in a patent specification that regards the prior art. Moreover, Mr. Boonaert never testified that any statement regarding the prior art was not verified. He testified, "Personally I did not verify that

point. Roquette must have verified it." (Excerpt from Boonaert Deposition Transcript, Exh. D hereto, at p. 78, line 13, to p. 79, line 7).

Similarly, the '777 patent comments with respect to the '146 patent that "[i]t has been verified that the size of the particles according to this process is, just as with the JP 80 [sic – 55] -36646 and JP 61-85330 processes described above, always very low, so much so that the mean diameter of the particles is between 50 and 75 microns." ('777 Patent, Exh. A to SPI Br., at Col. 4, ll. 6-12). Here too, SPI does not challenge either the accuracy or veracity of this comment. Rather, SPI merely asserts that the co-inventors of the '777 patent stated in their depositions that they either were not familiar with the '146 patent or did not personally verify the comment. (SPI Br. at p. 4). Notably, even that assertion by SPI is inaccurate. In fact, when SPI asked co-inventor Michel Serpelloni;

> How did you verify that the mean diameter of the particles according to those patents was at the value between 50 and 75 microns?

Mr. Serpelloni answered, "I don't recall." (Excerpt from Nov. 15, 2007 Serpelloni Deposition Transcript, Exh. E hereto, at p. 145, line 23 to p. 146, line 2).

SPI's contention that the '777 patent is unenforceable due to inequitable conduct merely because the inventors cannot recall whether or how they personally verified some comments made in the specification regarding prior art, which prior art was submitted to the PTO and which comments SPI does not challenge as inaccurate or misleading, is so lacking in merit that it is tantamount to bad faith.

IV. SPI'S ALLEGATIONS THAT ROQUETTE WITHHELD MATERIAL INFORMATION FROM TABLES 1 AND 2 OF THE '777 PATENT ARE BASELESS AND IMMATERIAL TO ANY CONTENTION OF INEQUITABLE CONDUCT

SPI at p. 5 of its brief arbitrarily infers from Table 1 of the '777 patent that Roquette concealed material information based solely on the fact that Table 1 includes some data as a range and other data as a single data point. Obviously, the only reasonable inference to be drawn from that fact is that when preparing Table 1, Roquette possessed a range of data for some of the reported properties and a single data point for others. In any event, SPI does not contend that any data, even if it was possessed and not included, would have been material and not merely cumulative to what is already presented in Table 1.

SPI also arbitrarily alleges inequitable conduct based on the use of the term "Commercial Product" in Table 1 associated with the listed comparative product obtained according to FR 2,571,045 because Roquette does not produce a commercial product under that French patent. Setting aside for the moment that SPI's observation falls far short of any reasonable basis for its claim of inequitable conduct, close inspection of Table 1 of the '777 patent reveals SPI's observation to be incorrect. The term Commercial product appears in the left-most column of Table 1 as a label for the associated row of data for "Apparent densities." Within that same section Table 1 also includes the term "100-200 micron cut" as a separate row of different data for apparent densities. Thus, Table 1 plainly provides two separate entries for the reported apparent densities, one corresponding to a preselected portion of a sample (i.e., a 100-200 micron cut),[6] and the other corresponding to the entire portion of the sample (i.e., the "Commercial product").

[6] A 100-200 micron cut corresponds to a portion taken from a sample which includes only those particles that are between 100 and 200 microns in size.

SPI's observation at page 5 of its brief that Table 2 of the '777 patent compares the compression force of mannitol made according to the invention with products other than spray-dried mannitol obtained by different methods is capricious and irrelevant. First, compression force does not appear as a recitation in any claim of the '777 patent, and as such, cannot be deemed material information. Moreover, the '777 patent makes clear that the purpose of Table 2 was to demonstrate that the product according to the invention yielded "harder tablets than with the different compressible products based on lactose or sucrose currently utilized in this application" -- i.e. the application of formulating tablets. ('777 Patent, Exh. A to SPI Br., at Col. 12, ll. 54-57) (emphasis added). Consistent with that stated purpose, Example 3 of the '777 patent identifies each comparative product represented in Table 2 by its commercial mark.

SPI's allegation that Table 2 does not compare the closest prior art ignores the '777 patent's explicitly stated and different purpose underlying the information presented in that Table, and fails to appreciate the fact that Table 2 includes only data for a property that is not recited in any claim.

ARGUMENT

Roquette acknowledges that Rule 15(a) of the Federal Rules of Civil Procedure instructs that leave to amend a party's pleading should be freely given when justice so requires. Although the Court has considerable discretion in considering a motion for leave to amend, the Supreme Court of the United States has instructed that a court may grant leave to amend "[i]n the absence of . . . undue delay, bad faith or dilatory motive on the part of the movant, repeated failure to cure deficiencies by amendments previously allowed, undue prejudice to the opposing party by virtue of allowance of the amendment, futility of the amendment, etc." *Foman v. Davis*, 371 U.S. 178, 182 (1962) (emphasis added).

While prejudice ordinarily is "the touchstone for the denial of an amendment," *Lorenz v. CSX Corp*., 1 F.3d 1406, 1414 (3d Cir. 1993), an amendment should be denied, without requiring the non-movant to demonstrate prejudice, when the amendment is grounded on bad faith or dilatory motive, truly undue or unexplained delay, or futility of the amendment. *Id*. (futility); *Inline Connection Corp. v. AOL Time Warner Inc*., 237 F.R.D. 361, 369 (D. Del. 2006) (bad faith, dilatory motive or truly undue or unexplained delay) (quoting *Rose Hall, Ltd. v. Chase Manhattan Overseas Banking Corp.*, 93 F.R.D. 858, 865 (D. Del. 1982)).

Moreover, an amended claim of inequitable conduct must be pled with particularity under Rule 9(b) of the Federal Rules of Civil Procedure, *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1356 (Fed. Cir. 2007); *Inline Connection Corp.*, 237 F.R.D. at 366-7, and in this case, because the deadline for amending pleadings expired on May 19, 2007 under the First Amended Scheduling Order (D.I. 111), it also must be supported by good cause under Rule 16(b)(4). Failure to satisfy either Rule 9(b) or 16(b)(4) is grounds for denial of SPI's motion for leave to amend. *See, e.g., Central Admixture Pharmacy Services, Inc.*, 482 F.3d at 1356-7 (affirming district court's dismissal of defendant's inequitable conduct claim for failure to plead with particularity).

I. SPI'S MOTION SHOULD BE DENIED BECAUSE THE AMENDMENT IS FUTILE

Futility of an amendment is measured by the same standard of legal sufficiency as applied under Rule 12(b)(6) of the Federal Rules of Procedure. *In re Burlington Coat Factory Sec. Litig.*, 114 F.3d 1410, 1434 (3d Cir. 1997). Accordingly, an amended pleading would be futile when it fails to state a claim upon which relief could be granted. *In re NAHC, Inc. Sec. Litig.*, 306 F.3d 1314, 1332 (3d Cir. 2002); see also *Warner-Lambert Co. v. TevaPharm., Inc*., 289 F. Supp. 2d 515, 544-5 (D.N.J. 2003) (denying defendant's motion for leave to amend its

answer to add inequitable conduct defense because "[t]here is absolutely no evidence pointing to an intent to deceive" and plaintiff "would be entitled to summary judgment in its favor on the defense"), *rev'd on other grounds*, 418 F.3d 1326 (Fed. Cir. 2005).[7]

Inequitable conduct in prosecution of a patent application requires clear and convincing evidence that an applicant concealed material information or submitted materially false information, combined with an intent to mislead or deceive the examiner. *McKesson Information Solutions, Inc. v. Bridge Medical, Inc.*, 487 F.3d 897, 913 (Fed. Cir. 2007). Information is material if a reasonable examiner would substantially likely consider it important in deciding whether to allow the application, and the intent element requires intent to deceive, not merely intent to withhold information. *Id*. "Intent to deceive cannot be inferred simply from the decision to withhold information where the reasons given for the withholding are plausible." *Id*.

Here, in literally every allegation that SPI asserts regarding inequitable conduct, SPI fails to allege any set of facts that could support a finding that information was material, that material information was withheld or misrepresented, or that anyone involved in prosecution of the '777 patent application acted with an intent to deceive the examiner. SPI's allegations of inequitable conduct are so lacking in merit that they are tantamount to bad faith.

For example, as we described above, applicants submitted a copy of JP 61-85331 to the examiner and the '777 patent specification accurately and fully describes the relevant portions of that document. SPI's allegations to the contrary, which are demonstrated herein to

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[7] We note that although in considering a motion for leave to amend under the legal standard for a motion to dismiss the Court would ordinarily accept as true all of the moving party's factual allegations and reasonable inferences therefrom, it would be impossible for the Court here to accept as true those specific allegations made by SPI which have been demonstrated to be patently false and contrary to the very publications to which those allegations pertain.

conceal more than half of what the '777 patent specification states regarding that Japanese application and misrepresent what that Japanese application actually discloses, are baseless, false, and misleading.

Regarding JP 61-85330, which again applicants submitted to the examiner and which the '777 patent specification accurately and fully describes, SPI's allegation of inequitable conduct relies entirely upon its incorrect citation of data that is in fact non-existent in that Japanese application.

Regarding SPI's allegations of inequitable conduct based upon the '777 patent specification's disclosures regarding JP 55-36646 and U.S. 3,145,146 and data provided in Table 1, SPI merely points to those disclosures and data without alleging that any of the information is false or misleading. Similarly with respect to Table 2 of the '777 patent specification, SPI merely observes that the comparative data there, which reports properties that are not recited in any claim of the patent, might have included additional data if the applicants had wished, without alleging that such additional data existed, that it would have been material, or that it was withheld with the intent to deceive the examiner.

In other words, SPI alleges at least seven different bases for its inequitable conduct claims without presenting a single accurate fact that might be relevant to an inquiry of concealment of material information, submission of materially false information, or an intent to deceive the examiner.

SPI's claims could not survive a motion to dismiss or a motion for summary judgment and, for that reason alone, its motion for leave to amend should be denied.

II. SPI'S MOTION ALSO SHOULD BE DENIED AS UNDULY DELAYED

A finding of undue and unexplained delay in seeking to amend a party's pleadings can, alone, justify the denial of that party's motion to amend. *E.g.*, *Inline Connection Corp.*, 237 F.R.D. at 369 (denying motion to add inequitable conduct allegations, without finding prejudice, based on delay of more than two years); *USX Corp. v. Barnhart*, 395 F.3d 161, 169 (3d Cir. 2004) (affirming district court's denial of motion to amend on grounds of unreasonable delay, without finding prejudice, where movant had sufficient knowledge more than a year before seeking leave to amend). As there is no clear threshold at which delay is deemed unreasonable, "the question of undue delay requires that we focus on the movant's reasons for not amending sooner." *Inline Connection Corp.*, 237 F.R.D. at 367-8.

Here, SPI's motion comes more than a year after filing its Answer and more than seven months after the deadline to amend or supplement pleadings in this case. Moreover, all of SPI's new allegations are based on information found in the '777 patent specification or certain of the prior art references cited on the face of the '777 patent – information which SPI had when it filed its first counterclaim of invalidity more than a year ago.

SPI's initial Answer, filed November 6, 2006, asserted a counterclaim of invalidity "for failure to satisfy the conditions of patentability specified in Title 35, U.S.C. §§ 101, 102, 103 and 112." (D.I. 15 at ¶ 23). SPI stated its basis for that counterclaim in its initial response to Roquette's contention interrogatory, stating:

> The claims are inoperable, anticipated, rendered obvious and/or indefinite, alone or in combination, by at least the following: . . . 5. References cited on the face of the '777 patent and/or referred to

> during prosecution of the '777 patent. (See SPI response to Interrogatory No. 7, Exh. F hereto).[8]

Thus, SPI confirms that at the time it filed is counterclaim of invalidity more than a year ago, it possessed the '777 patent and each of the references cited thereon – i.e. all of the information it now relies upon in seeking to add its new inequitable conduct theories.

SPI's sole explanation for its delay is that it required confirmation of its belief through the deposition testimony of the co-inventors, which depositions were taken in November, 2007. (Br. at 7-8). Attempting to validate that explanation, SPI relies heavily on this Court's decision in *Enzo Life Sciences, Inc. v. Digene Corp.*, 270 F. Supp. 2d 484 (D. Del. 2003). However, SPI's explanation and its reliance on *Enzo Life Sciences* are seriously misplaced.

In *Enzo Life Sciences*, this Court held that since inequitable conduct requires pleading with particularity, the movant's delay in seeking leave to amend its pleadings was justified because the defendant sought and obtained clear and convincing deposition testimony that supported its inequitable conduct claim. *See id*. For example, the movant in *Enzo Life Sciences* elicited deposition testimony from the inventors that directly contradicted two separate statements that the inventors had submitted to the PTO in a sworn declaration. *Id*. at 488.

Here, while SPI may have hoped to obtain relevant confirming testimony from the inventors, it failed in that attempt. The only deposition excerpts that SPI references in its brief consist of statements by the inventors that they did not, or do not recall, having personally verified some of the comments made in the '777 patent specification regarding the described and

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[8] After five months delay, and the necessity of a ruling from this Court that SPI must fully respond to Roquette's contention interrogatory, SPI finally provided its invalidity contentions which, with regard to the patents cited on the face of the '777 patent, remained virtually unchanged, alleging merely that "[t]he prior art references made of record during prosecution of the '777 patent disclose pulverulent mannitol and processes for its preparation such that each reference, individually or in combination, renders obvious claims 1-28 of the '777 patent."

submitted prior art. Unlike the facts in *Enzo Life Sciences*, that testimony in no way contradicts anything disclosed in the '777 patent or submitted to the PTO during its prosecution.

The facts in this case, instead, are analogous to those considered by this Court in *Inline Connection Corp. v. AOL Time Warner Inc.*, 237 F.R.D. 361, 369 (D. Del. 2006). In that case, the defendant sought leave to amend its pleadings to add new inequitable conduct theories and attempted to explain its delayed filing of its motion as necessitated by its attempts to obtain discovery from the patent owner. The Court found that the defendant's conduct revealed that it had possessed all the information it needed to assert its new inequitable conduct theories before it obtained the noted discovery. Accordingly, the Court rejected the defendant's explanation of delay and denied its motion to amend on the ground that the delay was undue. *Id.* at 368-9.

Like the facts in *Inline Connection Corp.*, SPI's conduct reveals that it possessed as early as November 6, 2006 all of the information it now relies upon in asserting its new inequitable conduct theories. SPI's sole explanation that it required confirmation through deposition testimony from the inventors should be rejected because (i) SPI places no meaningful reliance on any such testimony and (ii) the inventors' deposition testimony provided no such confirmation.

The Federal Circuit has cautioned that "an unsupported charge of 'inequitable conduct in the Patent Office' is a negative contribution to the rightful administration of justice." *Burlington Indus., Inc. v. Dayco Corp.*, 849 F.2d 1418, 1422 (Fed. Cir. 1988). Consistent with that advisement, courts do encourage a defendant to prudently "learn and confirm the bases of its allegations of inequitable conduct" in order to discourage "knee jerk, thoughtless, and poorly grounded assertions of inequitable conduct by defendants in patent infringement actions."

Biovail Labs. Int'l v. Andrx Pharm., LLC, 2007 WL 3231684, C.A. Nos. 05-586, 05-730, 06-620 (D. Del. May 4, 2007).

SPI's lengthy delay under the guise of seeking confirmation of its inequitable conduct theories through the inventors' depositions, followed by filing its motion to amend despite having failed to elicit any such confirmation in those depositions, disregards and even undermines the Federal Circuit's warning in *Burlington Indus., Inc.*, and results in an unduly delayed motion that still presents "thoughtless and poorly grounded assertions of inequitable conduct." SPI's conduct in this regard implicates considerations of bad faith.

SPI's motion to amend its pleading was unduly delayed, without reasonable explanation or good cause, for more than a year after SPI possessed the information it relies upon and more than seven months after deadline for amending its pleadings, and should be denied for that reason.

III. SPI'S MOTION ALSO SHOULD BE DENIED AS MADE IN BAD FAITH

As described at length above, SPI seeks to allege inequitable conduct based upon its own incomplete representation of what the '777 patent states, misrepresentation of what the prior art discloses, and without any meaningful statements of fact that might remotely support a finding of materiality, concealment or deceptive intent. Moreover, SPI's sole excuse for its lengthy delay is improper and in disregard of the clear warnings of this Court and the Federal Circuit.

Roquette considers the foregoing instances, individually and collectively, to be highly suggestive that SPI brought its present motion in bad faith or with dilatory motive. SPI's motion to amend also should be denied for that reason.

IV. SPI'S MOTION, IF GRANTED, WOULD PREJUDICE ROQUETTE

Denial of SPI's motion on any of the separate grounds urged above would not require a finding of prejudice to Roquette. Nevertheless, Roquette submits that it would in fact be significantly prejudiced were SPI permitted to amend its pleadings at this stage to include its multiple new inequitable conduct theories.

"A party is unduly prejudiced if amendment would cause surprise, result in additional discovery, or add cost in the preparation to defend against new facts or theories." *Inline Connection Corp.*, 237 F.R.D. at 369 (finding that defendant's amendment would introduce entirely new theories rather than mere supplementation, thus causing surprise and undue prejudice).

SPI's unexplained and undue delay in seeking to introduce entirely new theories of inequitable conduct, with the deadline for expert reports approaching, would require Roquette to engage in new, substantial and costly rework of its case. In light of SPI's scant bases for its proposed new theories, the consequential prejudice to Roquette would be disproportionate and undue.

CONCLUSION

For the foregoing reasons, Roquette submits that SPI's motion for leave to amend its pleadings to include inequitable conduct allegations should be denied.

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January 18, 2008

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on January 18, 2008 I electronically filed the foregoing with the Clerk of the Court using CM/ECF which will send notification of such filing to the following:

John W. Shaw
Jeffrey T. Castellano
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Additionally, I hereby certify that true and correct copies of the foregoing were caused to be served on January 18, 2008 upon the following individuals in the manner indicated:

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EXHIBIT A

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(54) Title of the invention Method of preparing direct tableting vehicle

(21) Patent Application No. S59-208637
(22) Filed on October 4, 1984

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Specification

1. Title of the invention

   Method of preparing direct tableting vehicle [II]

2. Claims

   (1) A method of preparing a direct tableting vehicle characterized by the fact that D-mannitol and hydrolyzed starch are spray dried.

   (2) The method of preparing a direct tableting vehicle according to Claim 1 wherein an aqueous solution or slurry of D-mannitol is used.

   (3) The method of preparing a direct tableting vehicle according to Claim 1 wherein an aqueous solution of hydrolyzed starch is used.

   (4) The method of preparing a direct tableting vehicle according to Claim 1 wherein 99.8 to 75 parts by weight of D-mannitol and 0.2 to 25 parts by weight of hydrolyzed starch are used.

   (5) The method of preparing a direct tableting vehicle according to Claim 1 wherein the spray drying is conducted at an exhaust heat temperature of 110 to 150 °C.

   (6) The method of preparing a direct tableting vehicle according to Claim 1 wherein hydrolyzed starch having a DE value of 5 or lower is used (the DE value is an indicator of the starch sugar quality level and expressed by directly reduced sugar (as glucose) / total solid content x 100).

3. Detailed explanation of the invention

   i) Purpose of the invention

   A] Scope of the invention

   The present invention relates to a method of preparing a direct tableting vehicle. More specifically, the present invention relates to a method of preparing a direct tableting vehicle characterized by the fact that D-mannitol and hydrolyzed starch are spray dried wherein the direct tableting vehicle consists of highly flowable, compressible, disintegrable,

and water-soluble D-mannitol/hydrated starch complex particles having no unfavorable effect on principal agents or main ingredients in manufacturing commercially available pharmaceutical products or food products of the principal agents or main ingredients.

B] Prior art technology

Commercially available D-mannitols are used by themselves as an alternate sweetener in pharmaceutical and food industries. However, when they are used as a vehicle, D-mannitols are rarely used by themselves, and are often combined with other highly compressible vehicles. For example, in order to obtain compressed tablets such as troches and chewable tablets, lactose is mainly used for obtaining water-soluble formulations primarily consisting of sugars (Pharmacia, 19 (12), 1268 (1983)). Other additives such as binders and fillers are combined in practice for obtaining formulations in which principal agents are stabilized. However, the principal agents may not be stabilized because of the lactose mixed in the former case and water-soluble formulations are not available because many binders and fillers are insoluble or hardly soluble in water in the latter case.

C] Problems overcome by the invention

If a water soluble direct tableting vehicle consisting of highly flowable, disintegrable, and compressible D-mannitol/hydrolyzed starch complex particles can be obtained without adversely affecting the features of D-mannitol such as cool and pleasant sweetness on the tongue, nonhygroscopicity, high melting point, high stability, and no incompatibility to the principal agents, it is preferable in view of reduced fluctuations in bioavailability of the principal agents due to formulation additives and easy analysis of formulations.

The inventors of the present invention assumed that the above drawbacks result from the poor bonding force of commercially available D-mannitols per se and enhanced the bonding force using spray drying. As a result, D-mannitol particles having somewhat satisfactory compressibility were obtained (an application filed). Then, the inventors came up with a combination of mixing of selected binders and spray drying in order to obtain compressible particles. Synthetic celluloses, natural proteins, and reins were selected among generally used water-soluble binders. D-mannitol was mixed with each of them and spray dried. The obtained particles were examined for compressibility. More specifically, an amount of 0.2 to 10 % of a binder such as hydroxypropyl cellulose, methyl cellulose, gelatin, or gum acacia was mixed with D-mannitol. The obtained formulations had unexpectedly low compressibility. Further research was conducted for such improvement and it was found that a desired direct tableting vehicle could be obtained by the production method described below, thereby completing the present invention.

ii) Structure of the invention

A] Problem resolution means

Set forth by embodiments, (1) a method of preparing a direct tableting vehicle characterized by the fact that D-mannitol and hydrolyzed starch are spray dried. (2) The method of preparing a direct tableting vehicle according to Claim 1 wherein an aqueous solution or slurry of D-mannitol is used. (3) The method of preparing a direct tableting vehicle according to Claim 1 wherein an aqueous solution of hydrolyzed starch is used. (4) The method of preparing a direct tableting vehicle according to Claim 1 wherein 99.8 to 75 parts by weight of D-mannitol and 0.2 to 25 parts by weight of hydrolyzed starch are used. (5) The method of preparing a direct tableting vehicle according to Claim 1 wherein the spray drying is conducted at an exhaust heat temperature of 110 to 150 °C. (6) The method of preparing a direct tableting vehicle according to Claim 1 wherein hydrolyzed starch having a DE value of 5 or lower is used (the DE value is an indicator of the starch sugar quality level and expressed by directly reduced sugar (as glucose) / total solid content x 100).

The D-mannitol used in the present invention can be any D-mannitol obtained by any of the following methods: liquid extraction from seaweed, ammonia electroreduction of a glucose solution, contact reduction of a sucrose solution and pursuant to Japanese Pharmacopoeia, Japanese Standards of Food Additives, USP standards, and BP standards.

Hydrolyzed starch is a sugar composite consisting of oligosaccharides of momo- to hepta-saccharides obtained by hydrolyzing starch as a row material in roasting, roasting with oxygen, acid decomposition, or oxygen decomposition. Preferable results can be obtained when the hydrolyzed starch is a sugar composite having a DE (dextrose equivalent) value of 5 or lower because the sugar composite has a small amount of reducing end groups and has no influence on the principal agents of pharmaceutical products and others, low hygroscopicity, and high protective colloid property.

For spray drying a mixture of D-mannitol and hydrolyzed starch, an aqueous solution or slurry of D-mannitol is added to an aqueous solution of hydrolyzed starch to a final concentration of 20 to 50 weight/weight %. The preparation condition can include heating to 60 to 80 °C.

For obtaining D-mannitol/hydrolyzed starch complex particles, 99.8 to 75 parts by weight of D-mannitol and 0.2 to 25 parts by weight are used. When more than 25 parts by weight of hydrolyzed starch is used, the viscosity of a solution or slurry obtained after the mixing is rapidly increased, which lowers the drying process performance. In addition, more particles adhere to the drying machine, which disadvantageously lowers the drying yield. Furthermore, the dried product is highly hygroscopic and the direct tableted drug disintegrates slowly. In consideration of drying ability, preparation conditions, formulation quantities including disintegration property and compressibility,

and further uniform content of principal agents or main ingredients due to adjustable particle sizes, the most preferably result can be obtained using 99.8 to 75 parts by weight of D-mannitol and 0.2 to 25 parts by weight.

Regarding spray drying conditions in the drying process of an aqueous solution or slurry obtained by mixing D-mannitol and hydrolyzed starch for obtaining D-mannitol/hydrolyzed starch complex particles, the exhaust heat temperature can be selected in a relatively wide range of 110 to 150 °C. This gives a high degree of freedom to the drying process. Preferably, in combination with the concentration of the aqueous solution or slurry, any form of particles ranging from fine granules to fine powder and any particle size distribution can be obtained on an arbitrary basis. When the drying temperature is lower than 110 °C or higher than 160 °C, it is difficult to obtain an excellent product because among the formulation properties of a product obtained, the compressibility depends on the prevalence of crystals in X-ray crystallography.

B] Efficacy

When an aqueous solution or slurry of D-mannitol is spray dried with the addition of hydrolyzed starch having a DE value of 5 or lower, fine granules or fine power can be obtained. The X-ray diffractometric comparison of diffraction crystal face distances [Å] between such products and test products obtained in References showed surprising results [Table VII]. The products obtained in the present invention had d values of 5.33 [Å] and 5.15 [Å] while poorly compressible test products in References using D-mannitol powder, D-mannitol/hydrolyzed starch mixed power, or D-mannitol/hydrolyzed starch wet-granulated powder had a d value of 5.33 [Å] only. A poorly compressible test product in a Reference in which D-mannitol powder was melted at up to 160 °C had a d value of 5.15 [Å] only.

Strong correlation was found between excellent compressibility and d values of 5.33 [Å] and 5.15 [Å] in the products obtained in embodiments of the present invention although their mechanism of action was not clarified.

In any event, in the products obtained as in the embodiments of the present invention, in other words with the addition of hydrolyzed starch, the state of solution of D-mannitol and hydrolyzed starch and the spray dry conditions cause concerted interaction. The obtained fine powder or fine granules shown in Fig.1 of “the drawing” presumably allows dense packing and smooth propagation of compression, and no unfavorable properties in manufacturing including phenomenon such as capping and cracking are shown.

C] Embodiments

Embodiments and References are given hereafter for understanding the present invention.

Embodiment 1

An amount of 9.95 kg of Japanese Pharmacopoeia D-mannitol was added to 25 kg of 0.2 w/w % solution of hydrolyzed starch having a DE value of 3.2 and heated to 75 °C while stirring to prepare an aqueous solution. The solution was held at a solution temperature of 70 to 75 °C and spray dried in the rotating disk contactor process at an input heat temperature of 221 to 225 °C and an exhaust heat temperature of 124 to 130 °C to obtain 9.62 kg of fine powder.

Embodiment 2

An amount of 9.5 kg of Japanese Pharmacopoeia D-mannitol was added to 20.0 kg of 2.5 w/w % solution of hydrolyzed starch having a DE value of 1.9 and mixed to a homogeneous mixture. The mixture (solution temperature of 70 to 75 °C) was spray dried in the rotating disk contactor process at an input heat temperature of 216 to 219 °C and an exhaust heat temperature of 124 to 128 °C to obtain 9.58 kg of fine powder.

Embodiment 3

An amount of 8.5 kg of Japanese Pharmacopoeia D-mannitol was added to 15.0 kg of 10.0 w/w % solution of hydrolyzed starch having a DE value of 1.9 and mixed to a homogeneous mixture. The mixture (solution temperature of 20.6 °C) was spray dried in the pressurized nozzle process at an input heat temperature of 201 to 206 °C and an exhaust heat temperature of 120 to 126 °C to obtain 9.48 kg of fine granules.

Embodiment 4

An amount of 7.5 kg of Japanese Pharmacopoeia D-mannitol was added to 25.0 kg of 10.0 w/w % solution of hydrolyzed starch having a DE value of 4.6 and mixed to a homogeneous mixture. The mixture (solution temperature of 21.2 °C) was spray dried in the pressurized nozzle process at an input heat temperature of 199 to 212 °C and an exhaust heat temperature of 121 to 123 °C to obtain 9.61 kg of fine granules.

Reference 1

Japanese Pharmacopoeia D-mannitol screened with a 100 mesh.

Reference 2

Powder obtained by mixing 4.25 kg of Japanese Pharmacopoeia D-mannitol and 0.75 kg of hydrolyzed starch having a DE value of 1.9 to a homogeneous mixture.

Reference 3

An amount of 0.6 kg of water was added to 0.75 kg of hydrolyzed starch having a DE value of 1.9 to prepare a sticky paste. The paste was added to 4.25 kg of Japanese Pharmacopoeia D-mannitol and mixed to a homogeneous mixture. The mixture was pulverized and granulated using a 30 mesh screen, shelf-dried, and then sized using a 30 mesh screen to obtain 4.66 kg of fine granules.

Reference 4

Japanese Pharmacopoeia D-mannitol was placed in a porcelain dish, heated to 168 °C for melting, cooled, pulverized, and sized using a 30 mesh screen.

Physical properties and formulation properties of the products obtained in Embodiments of the present invention and References were examined. The results are shown in Tables I to VI. Additionally, Table VII shows the X-ray diffractometry results.

Table I Physical properties

physical property / sample	bulk specific volume (ml/g)	particle size (%)			repose angle (°)	drying loss[1)] (%)	hygroscopicity[2)]	
		32 mesh on	32-150 mesh	200 mesh th			moisture pickup (%)	appearance change
Embodiment 1	1.91	0	26	89	34	0.08	0.02	N/A
Embodiment 2	2.36	0	21	73	38	0.16	0.41	N/A
Embodiment 3	2.08	1	86	9	32	0.18	0.81	N/A
Embodiment 4	2.13	1	91	4	32	0.36	1.36	N/A
Reference 1	1.76	0	8	84	44	0.08	0.05	N/A
Reference 2	1.91	0	5	89	45	0.86	3.65	solidified
Reference 3	1.93	3	92	1	37	0.22	1.09	N/A
Reference 4	1.68	0	11	89	40	0.02	0.03	N/A

1) An amount of 1,000 g of sample was precisely weighed in a weighing bottle and dried at 105 °C for three hours. Then, the weight loss was determined.

2) The sample was dried at 105 °C for three hours. Approximately 1, 000g of the anhydride was precisely weighed and allowed to stand at 40 °C and 75 % RH for 120 hours. The sample weight was measured and the weight gain was assumed to be the moisture pickup. Meanwhile, the appearance was observed for any change.

Table II Formulation characteristics: compressibility

tableting pressure / sample	1,000 (kg/cm^2)	2,000 (kg/cm^2)	3,000 (kg/cm^2)
Embodiment 1	8.0	14.4	18.9
Embodiment 2	9.1	16.4	21.3
Embodiment 3	10.4	18.8	25.8
Embodiment 4	13.8	22.6	28.7
Reference 1	3.2	incompressible due to capping	incompressible due to capping
Reference 2	3.9	6.4	incompressible due to capping
Reference 3	7.8	10.9	incompressible due to capping
Reference 4	incompressible due to capping	incompressible due to capping	incompressible due to capping

Numbers in the table are Monsanto hardness (kg)

Tableting conditions:

With the addition of magnesium stearate to 1%, each sample was statically compressed into tablets in a Brinell hardness tester (ex. Yonekura Seisakujo) with a 10 mm ϕ parallel punch and set for 300 mg per tablet.

1. Tablet hardness

Twenty tablets were measured using a Monsanto harness meter and the average was obtained.

2. Tablet thickness

Twenty tablets were measured using a micrometer and the average was obtained.

3. Disintegration test

The average time measured pursuant to the disintegration test of Japanese Pharmacopoeia. However, no disk was used.

4. Formulation weight

Twenty tablets were measured using a micrometer and the average was obtained.

Table III-1 Formulation characteristics: changes in formulation characteristics in accelerated test (formulation hardness adjusted for 5 to 8 kg)

	Tablet characteristics value	Monsanto Hardness (Kg)			disintegrating time (min)			weight (mg)		
sample \ acceleration condition / tableting pressure (kg/cm²)		Initial	40°	40° 75%RH	Initial	40°	40° 75%RH	Initial	40°	40° 75%RH
Embodiment 1	1,000	8.0	8.1	7.9	2.6	2.5	2.9	301	301	301
Embodiment 2	500	5.6	5.5	5.6	2.8	2.7	3.0	299	298	300
Embodiment 3	500	6.0	5.8	5.9	3.1	3.1	2.9	301	301	301
Embodiment 4	500	6.7	6.5	8.9	3.5	3.4	3.8	299	299	299
Reference 1	1,500	5.5	5.6	5.8	1.8	1.6	2.0	300	300	300
Reference 2	2,000	6.4	6.7	6.7	3.3	5.0	4.7	298	298	300
Reference 3	1,000	7.8	7.4	7.3	3.5	4.6	4.5	299	299	300
Reference 4	--	uncompressible due to capping								

Table III-2 Formulation characteristics: changes in formulation characteristics in accelerated test (formulation hardness adjusted for 13 to 17 kg)

	Tablet characteristics value	Monsanto Hardness (Kg)			disintegrating time (min)			weight (mg)		
sample \ acceleration condition / tableting pressure (kg/cm²)		Initial	40°	40° 75%RH	Initial	40°	40° 75%RH	Initial	40°	40° 75%RH
Embodiment 1	1,500	13.2	12.8	13.5	6.8	6.6	6.9	299	299	299
Embodiment 2	1,500	16.4	16.6	16.5	7.0	7.1	7.0	301	301	301
Embodiment 3	1,000	15.4	15.0	15.1	7.0	6.8	6.6	300	300	300
Embodiment 4	3,000	16.9	17.0	17.2	7.4	7.1	7.3	300	300	300
Reference 1	--	uncompressible due to capping								
Reference 2	--	uncompressible due to capping								
Reference 3	--	uncompressible due to capping								
Reference 4	--	uncompressible due to capping								

In the accelerated test, tablets of each sample were wrapped with a 7 μ polycello and tested at 40° and at 40° and 75 % RH for 30 days.

Table IV Exemplary use Formula

	Embodiments		principal agent and sample amount		sucrose fatty acid ester	total
	No.	sample amount				
Formula 1	2	462 g	bicarbonate of soda	420 g	18 g	900 g
Formula 2	3	462 g	ascorbic acid	420 g	18 g	900 g
Formula 3	4	462 g	acetylsalicylic acid	420 g	18 g	900 g

Table V Formulation characteristics of Exemplary use

formula No. / Tablet characteristics test	Formula 1	Formula 2	Formula 3
tablet average weight	300.8 mg	302.0 mg	301.6 mg
disintegration time (water)	7.2 min	6.4 min	5.3 min
average Monsanto hardness of 20 tablets	11.8 kg	13.1 kg	9.1 kg
average thickness of 20 tablets	3.02 mm	3.34 mm	3.28 mm
standard deviation	3.22 mg	2.98 mg	3.86 mg

Exemplary use

The samples obtained in Embodiments were mixed with principal agents such as ascorbic acid, bicarbonate of soda, or acetylsalicylic acid and directly tableted.

<Formula>

The power or granular samples obtained in Embodiments 2, 3, and 4 were mixed with principal agents according to the formulae in Table IV to a homogenized mixture.

<Tableting conditions>

A tablet weight was set for 300 mg. A tablet diameter 9 mm ϕ R type punch was prepared and the tbaleting was conducted at a pressure of 2,500 kg/cm^2 and at 30 rpm in a tableting machine Model HT/P18 (ex. Hata Tekkojo).

<Results>

The tablets obtained in the exemplary use test had the following characteristic values, which complied with Japanese Standards for Pharmaceutical Tablets (Table V).

<Accelerated test of principal agent-mixed formulations in exemplary use>

The tablets of Exemplary use Formula 2 was wrapped with a 7 μ polycello and tested at 40°C for 30 days.

<Results>

The results are shown in Table VI. Changes in the principal agent content were presumably small.

Table VI Change in the principal agent content in Exemplary use Formulation in Accelerated test

item / formula No.	condition	ascorbic acid content (%)
Formula 2	Initial	99.2
	40°, 3 months	97.2

Table VII X Ray diffractometry

Example	I ratio	Reference	I ratio
1	0.9	1	--
2	0.7	2	--
3	0.7	3	--
4	0.6	4	--

X Ray diffractometry: An X-ray diffracting device (Model RAD-20IA ex. Rigaku-Denki), was used with the target on Cu and at 30 KV, 20 mA.

I ratio : I_1/I_0 wherein I_0 is a strength at a d value of 5.33 and I_1 is a strength at a d value of 5.15. The symbol "--" indicates no I ratio.

As apparent from Table I, the products obtained in Embodiments of the present invention had a relatively low bulk specific volume of 1.89 to 2.36 ml/g and an excellent repose angle of 32° to 38°. They also had low hygroscopicity.

When the products obtained in Embodiments of the present invention were compressed into tablets at a tableting pressure of 1,000 to 3,000 kg/cm^2, the hardness was increased as the tableting pressure was raised. Capping or cracking, which is observed in the case of low compressibility, did not occur (Table II). In the test products having a Monsanto hardness adjusted for 5 to 8 kg, initial short disintegration time and hardness were unchanged under the acceleration conditions such as heating or heating/moisturizing. Even the formulations having a Monsanto hardness adjusted for 13 to 17 kg showed the same tendency (Tables III-1 and III-2).

When the products obtained in Embodiments of the present invention were formulated with principal agents such as antacid, vitamins, or analgesic (Table IV) and directly tableted, fast disintegrating formulations complying with the Tablet Disintegration Test of Japanese Pharmacopoeia were obtained. No unfavorable phenomenon in tablet compression such as capping was observed. Formulations having excellent flowability and small fluctuations in formulation weight were obtained (Table V).

iii) Efficacy of the invention

Data regarding flowability, disintegration property, and compressibility of the products obtained by the present invention and data regarding disintegration property and compressibility of the products obtained by directly tableting the powder of the products obtained by the present invention and mixed with principal agents or antacid are given above. Commercially available D-mannitol powder has poor compressibility. However, when the requirements for the additive rate of hydrolyzed starch, state of solution of D-mannitol and hydrolyzed starch, and spray dry conditions are satisfied, D-mannitol/hydrolyzed starch complex particles having compressibility as a direct tableting vehicle can be obtained and the obtained particles can range from fine granules to fine powder and have compressibility adjusted on an arbitrary basis. Formulations obtained by the present invention have favorable flowability, disintegration property, and compressibility for preparing formulations. When the product of the present invention is in practical use for example with ascorbic acid, the above characteristics are unchanged. The accelerated test also showed favorable results (Table VI). Therefore, the vehicle consisting of D-mannitol/hydrolyzed starch complex particles can usefully be used as a direct tableting vehicle having excellent flowability, disintegration property, and compressibility with no influence on the properties of D-mannitol and lead to great efficacy on drug manufacturing process.

4. Brief explanation of the drawings

Fig.1 is a scanning type electron microscopic picture regarding Embodiment 2 of the present invention, showing partly hollow spherical fine granules. Fig.2 is a scanning type electron microscopic picture regarding Reference 1, showing columnar crystals. The particle size was noted.

Applicant

Fuji Chemical Industry

Fig.1

Fig.2

Amendment (formal)

February 13, 1985

To: Mr. Manabu Shiga, Commissioner of Patent Office

1. Case ID Patent Application No. S59-208637
2. Title of the invention Method of preparing direct tableting vehicle
3. Amender
   Relation to the case Patent Applicant
   Address 55 Yokohouonji, Kamiichi-machi, Nakaniikawa-gun, Toyamaken
   Name Fuji Chemical Industry
   Yasumasa Nishida, President
4. Date of Order for Amendment (Mailing date) January 29, 1985
5. Object for Amendment
   Title of the invention in Application Form and Specification
6. Content of Amendment
   In the attachment

Attachment

I In Application Form, 1. Title of the invention, “Method of preparing direct tableting vehicle [II]” is changed to “Method of preparing direct tableting vehicle” with “[II]” being deleted.

II In Specification, page 1, 1. Title of the invention, “Method of preparing direct tableting vehicle [II]” is changed to “Method of preparing direct tableting vehicle” with “[II]” being deleted.

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭61－85331

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審査請求　未請求　発明の数 1　（全8頁）

⑭発明の名称　直打用賦形薬の製造法

⑳特　願　昭59－208637
㉒出　願　昭59(1984)10月4日

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明　細　書

1．発明の名称

直打用賦形薬の製造法（II）

2．特許請求の範囲

(1) D－マンニトールとでん粉加水分解物とを噴霧乾燥することを特長とする直打用賦形薬の製造法。

(2) D－マンニトールの水溶液又はスラリーを用いる特許請求の範囲第1項記載の直打用賦形薬の製造法。

(3) でん粉加水分解物の水溶液を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法。

(4) D－マンニトール88.8～75重量部とでん粉加水分解物 0.2～25重量部を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法。

(5) 噴霧乾燥を排熱温度 110～130 ℃で行う特許請求の範囲第1項記載の直打用賦形薬の製造法。

(6) でん粉加水分解物のDE値（但し、DE値はでん粉糖の品位の表示であって、直接還元糖（ぶどう糖として）／全固形分×100 で表わされる）が5以下であるものを用いる特許請求の範囲第1項記載の直打用賦形薬の製造法。

3．発明の詳細な説明

イ）発明の目的

A］産業上の利用分野

本発明は直打用賦形薬の製造法に関するものである。更に詳しくは、D－マンニトールとでん粉加水分解物を噴霧乾燥することを特長とする直打用賦形薬の製造法に関するものであって、医薬上医薬品の主薬、食品の主材の賦形化に際して、それら主薬、主材に何等の好ましからざる作用を及ぼすことなく、流動性、成型性、崩壊性の良い水可溶性のD－マンニトール・でん粉加水分解物複合粉粒よりなる直打用賦形薬の製造法に関するものである。

〔B〕従来の技術

Dーマンニトールは医薬品、食品産業分野において賦形剤として単独で広く用いられている。しかしながら、賦形薬として用いる場合、Dーマンニトール単独では使用されることは少なく、例えばトローチ、チュアブル錠等の圧縮錠を得るには、圧縮性の良い他の賦形薬と配合して用いられることが多い。結果を主体にして水可溶性の製剤を得ようとする場合、主に乳糖が用いられる(ファルマシア，19(12)，1268(1983))。又、主薬安定形の製剤を得るには、結合剤、フィラーなど他の添加物を配合して用いられているのが実情である。しかしながら、前者にあっては乳糖配合が原因して、医薬品の主薬に対して安定性を欠く場合があり、後者の場合には結合剤、フィラーの多くは水不溶性又は難溶性のものであるため、水可溶性製剤を得ることができない欠点がある。

〔C〕発明が解決しようとする問題点

Dーマンニトールの持つ特性、即ち苦ざわりの良い涼しい甘味，非吸湿性，高融点，良好な安定性，主薬との配合禁忌がないなどの性質に何等悪影響を及ぼすことがなく，流動性，崩壊性，成型性の良好なDーマンニトール・でん粉加水分解物複合物質よりなる水可溶性の直打用賦形薬が得られれば，製剤添加物に起因する生体の生体利用率のバラツキが少なく，又製剤分析を容易に行える点でも好ましいと考える。

本発明者らは上記の欠点の原因は前項のDーマンニトール自身の結合力の弱さに起因すると考え、その結合力の増強を噴霧乾燥技術によって計り，やや満足すべき成型性を有するDーマンニトール粉粒を得た〔出願中〕。しかし，成型性を有する粉粒を得るため、選ばれた結合剤と配合することと、それに加えて噴霧乾燥技術を組合せることを思いたった。結合剤として使用されるもののうち，水可溶性のものの中から，合成セルロース系、天然蛋白質並びに樹脂類を選び，それらの各々とDーマンニトールとの混合物を噴霧乾燥させ、得られた粉粒の成型

性を調べた。即ち，結合剤のヒドロキシプロピルセルロース，メチルセルロース，ゼラチン，又はアラビアゴムの 0.2～10%をDーマンニトールと配合させたが，予期に反し得られた製剤の成型性は乏かった。従って更にこれらの改善に関し鋭意改良研究を行って，次に述べるような製造法によって初めて所望の直打用賦形薬を得ることが出来ることを知り、本発明を完成するに至った。

〔D〕発明の構成

〔A〕問題点を解決するための手段

実施態様で示せば，(1) Dーマンニトールとでん粉加水分解物とを噴霧乾燥することを特徴とする直打用賦形薬の製造法，(2) Dーマンニトールの水溶液又はスラリーを用いる特許請求の範囲第1項記載の直打用賦形薬の製造法，(3) でん粉加水分解物の水溶液を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法，(4) Dーマンニトール99.8～75重量部とでん粉加水分解物 0.2～25重量部を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法，(5) 噴霧乾燥を排熱温度 110～150 ℃で行う特許請求の範囲第1項記載の直打用賦形薬の製造法，(6) でん粉加水分解物のDE値（但し、DE値はでん粉糖の品位の表示であって、直接還元糖（ぶどう糖として）／全固形分×100 で表わされる）が5以下であるものを用いる特許請求の範囲第1項記載の直打用賦形薬の製造法によるものである。

本発明に用いられるDーマンニトールは海藻からの液体抽出法，ぶどう糖液のアンモニア電解還元法，もち糖溶液の接触還元法のいずれかの方法によって得られた日本薬局方，食品添加物公定書規格，USP規格，BP規格に適するDーマンニトールであればよい。

でん粉加水分解物とは，原料のでん粉を酸処法，酸素添加処法，酵分解法あるいは酵素分解法により加水分解された部類から7個のブドウ糖からなる縮合成物であって、それら組成物の内DE値（Dextrose Equivalent）が5以下

の低ＤＥ値でん粉加水分解物のうちから選ばれれば、縮合成物の還元性末端基が少ないことを意味するので、保存品等の変質に対し、なんらの影響を及ぼさないため、更に吸湿性が少なく、保護コロイド性が大きいために好ましい結果をもたらす。

Ｄ－マンニトールとでん粉加水分解物との混合物を噴霧乾燥する場合、でん粉加水分解物の水溶液に、Ｄ－マンニトールの水溶液又はスラリー液のいずれかを加えて最終の濃度20～50重量／重量％に調製されるが、60～80℃に加温する条件を加えて調製しても良い。

Ｄ－マンニトール・でん粉加水分解物複合粉末を得る場合、Ｄ－マンニトール粉末99.5～75重量部、でん粉加水分解物0.2～25重量部とを用いるが、25重量部以上のでん粉加水分解物を使用すれば、混合調製して得られる水溶液又はスラリー液の粘度が急に上昇しはじめるため、乾燥工程においてその流動が低下する上、乾燥機壁への粘着付着がおくなり、乾燥効率を低下さ

せるような工程上の不利をもたらすばかりか、乾燥後得られる製品は吸湿性が大になるうえ、粒打錠剤の崩壊が遅くなる欠点が生じてくる。従って乾燥能力、調製による粘度条件や、崩壊性、成形性など製剤品質、更に粒子径が自由に調節できる点による主旨、主特の合成約一部の改良可能なことを考慮すれば、Ｄ－マンニトール95.5～75重量部と、でん粉加水分解物0.2～25重量部とを使用するのが最も好ましい結果が得られる。

Ｄ－マンニトール・でん粉加水分解物複合粉末を得るに際しての、Ｄ－マンニトールとでん粉加水分解物を混合調製して得られる水溶液又はスラリー液の乾燥工程における噴霧乾燥条件としては、操作温度 110～150 ℃の比較的広い範囲で選ぶことができる。このことは乾燥工程における自由度が大きくなることを意味するので、水溶液又はスラリー液の濃度の条件と組合せて、得られる粒形としては細粒から顆粒状粉体が、又、結晶分布の巾さえもが自由に選べ大

まで溶解を行った参考例の圧縮成型性の不良な試験品はd値が5.15［Å］にのみ認めるにしかすぎない。

このように、本発明の実施例で得られた製品が成型性の良好な特性を有することと、又線回折法においてd値が5.33［Å］、5.15［Å］に伴って存在することを認めることとの間に強い相関性を発見したにも関わらず、それらが詳細機序をここで明らかにすることはできなかった。

然しながらいずれにしても、本発明の実施例のごとくにして得られた製品、即ちでん粉加水分解物を配合するとき、Ｄ－マンニトール、でん粉加水分解物の溶解状態、噴霧乾燥条件とが積極的に作用し、得られた顆粒状粉末又は「摘要」の第１図に示す顆粒が適充填性と圧縮の円滑な保持性を与えるが故に、製剤上望ましくない特性、即ちキャッピング、クラッキングなどの現象を示すことはないものと考えられる。

Ｃ）実施例

以下に本発明についての理解を便ならしめるための実施例、参考例を記す。

実施例1

DE値3.2のでん粉加水分解物の0.2w/w%水溶液25kgに日局D－マンニトール9.95kgを加え、撹拌しながら液温75℃に加温して水溶液となす。この溶液を液温75～75℃に保持しながら、入熱温度221～225℃，排熱温度125～130℃で回転円板法にて噴霧乾燥し、9.82kgの細粒状粉末を得た。

実施例2

DE値1.9のでん粉加水分解物の2.9w/w%水溶液20.0kgに日局D－マンニトール9.5kgを加え均一混和する。この混和液（液温70-75℃）を入熱温度216～219℃、排熱温度124～126℃で回転円板法にて噴霧乾燥を行い9.50kgの細粒状粉末を得た。

実施例3

DE値1.9のでん粉加水分解物の10.0w/w%水溶液15.0kgに日局D－マンニトール9.5kgを

加え均一混和する。この混和液（液温20.8℃）を入熱温度201～206℃，排熱温度120～126℃で加圧ノズル法にて噴霧乾燥を行い，9.46kgの細粒を得た。

実施例4

DE値4.6のでん粉加水分解物の10.0w/w%水溶液25.0kgに日局D－マンニトール7.5kgを加え均一混和する。この混和液（液温21.2℃）を入熱温度199～212℃、排熱温度121～123℃で加圧ノズル法にて噴霧乾燥を行い、9.61kgの細粒を得た。

参考例1

日局D－マンニトールの100メッシュ通過粉末。

参考例2

日局D－マンニトール4.25kgとDE値1.9のでん粉加水分解物0.75kgを均一に粉末混合して得た粉末。

参考例3

DE値1.9のでん粉加水分解物0.75kgに水

0.6kgを加え糊状液とし、これを日局D－マンニトール4.25kg中へ加え均一練合する。この練合物を30メッシュスクリーンを用いて湿式造粒を行い，棚式乾燥し、更に30メッシュ篩過整粒を行って、4.66kgの細粒を得た。

参考例4

日局D－マンニトールを磁製皿に取り、約169℃に加熱 融させ，冷後粉砕し、30メッシュ篩過整粒した。

本発明の実施例、参考例で得た製品の物性試験並びに製剤特性試験を行って、その結果を表I～表Ⅶに示した。又、表Ⅷに X線回折法で得られた結果を示した。

表I　物性値

試料＼物性	嵩比容 (ml/g)	粒度 (%) 32mesh on	32-150mesh	200mesh 下	安息角 (°)	乾燥減量 (%)	吸湿性 吸湿増(%)	外観変化
実施例1	1.91	0	36	63	34	0.08	0.92	なし
〃 2	2.38	0	21	29	38	0.18	0.41	なし
〃 3	2.06	1	39	9	32	0.18	0.81	なし
〃 4	2.13	1	51	4	32	0.36	1.15	なし
参考例1	1.76	0	5	84	44	0.08	0.45	なし
〃 2	1.91	0	5	89	45	0.30	3.65	固化
〃 3	1.93	3	92	1	37	0.22	1.08	なし
参考例4	1.58	0	11	89	40	0.02	0.05	なし

1）行程瓶に試料1.000gを正確に量り、105 ℃ ± 3時間乾燥し、その減量を求める。

2）試料を105 ℃ ± 3時間乾燥し、吸水物としたもの約1.000gを試験に採り、40°-75%RH下に120時間放置した後、試料重量を測定し、重量の増量分を吸湿量とする。又、このときの外観変化についても同時に観察する。

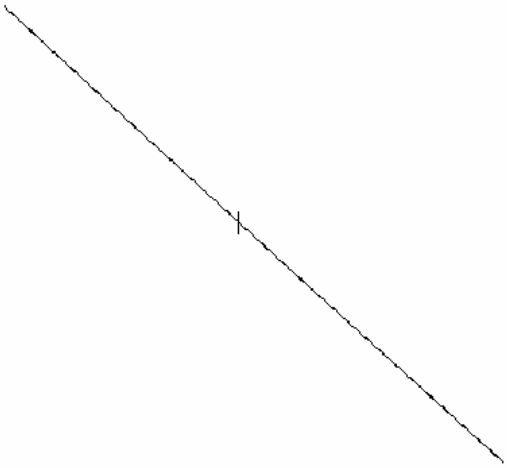


図5

表8　製剤物性試験：圧縮成型機

試料 ＼ 打錠圧	1,000 (kg/cm²)	2,000 (kg/cm²)	3,000 (kg/cm²)
実施例 1	8.0	14.4	18.9
〃 2	9.2	16.4	21.3
〃 3	10.4	18.8	25.8
〃 4	13.8	22.6	28.7
参考例 1	3.2	表面不均一	表面不均一
〃 2	3.3	表面不均一	表面不均一
〃 3	7.8	10.9	表面不均一
〃 4	表面不均一	表面不均一	表面不均一

表中の数値はモンサント硬度（kg）

図6

打錠条件：

各試料にステアリン酸マグネシウムを1%添加し、10mmø平杵を用い、1錠300mgの錠重で、ブリネル硬さ試験機（木倉製作所製）を用い、静的圧縮打錠を行う。

錠剤の物性試験方法：

1.錠剤の硬度

モンサント硬度計を用い、20錠についてn=5測定し、平均値で求める。

2.錠剤の厚み

マイクロメーターを用い、20錠について各々測定し、平均値で求める。

3.崩壊試験

日本薬局方の崩壊試験法に準じて測定した平均時間。但し、補助盤は用いない。

4.錠剤の重量

20錠についてn=5測定し、その平均値で求める。

表8－1　錠剤物性試験：圧縮試験による錠剤物性の変化
（錠剤硬度5～8kgに調整した場合）

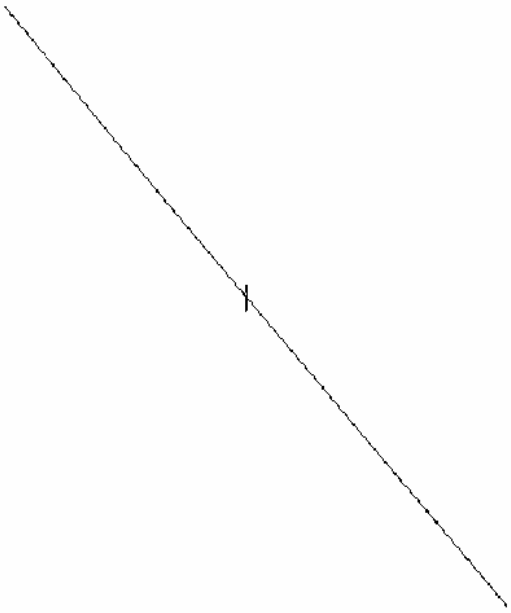
試料 ＼ 錠剤物性値	打錠条件 (kg/cm²)	モンサント硬度(kg) Initial	モンサント硬度(kg) 40° 75%RH	崩壊時間(分) Initial	崩壊時間(分) 40°	崩壊時間(分) 40° 75%RH	厚さ Initial	厚さ 40°	厚さ 40° 75%RH
実施例1	1,000	8.0	8.1	2.6	2.5	2.8	3.01	3.01	3.01
〃 2	500	5.5	5.5	2.8	2.7	3.0	2.99	2.98	3.00
〃 3	500	6.0	5.8	2.1	2.1	2.9	3.01	3.01	3.01
〃 4	500	6.7	6.5	2.5	2.4	3.0	2.99	2.99	2.99
参考例1	1,500	5.5	5.0	1.6	1.5	2.0	3.00	3.00	3.00
〃 2	2,000	6.4	6.2	3.3	3.0	4.7	2.98	2.98	3.00
〃 3	1,000	7.8	7.4	3.5	3.3	5.5	2.99	2.99	3.00
〃 4	——	キャッピングが生じ成型不可能							

図8

表Ⅳ－2　製剤特性試験：連続試験による製剤特性の変化
（錠剤硬度13～17kgに調整した場合）

錠剤特性 / 試験時間		モンサント硬度(kg) Initial	モンサント硬度(kg) 40°/75%RH	崩壊時間(分) Initial	崩壊時間(分) 40°/75%RH	重量 Initial	重量 40°/75%RH (mg)
実施例1	1,500	13.2	13.5	6.8	6.9	299	299
〃 2	1,500	16.4	16.8	7.0	7.0	301	301
〃 3	1,000	15.4	15.8	6.8	6.8	300	300
〃 4	1,000	16.9	17.2	7.4	7.3	300	300
参考例1	—	キャッピングが生じ錠剤不可能					
〃 2	—	〃					
〃 3	—	〃					
〃 4	—	〃					

崩壊試験は、各試料の錠剤を7ヶポリセロ袋詰し、40°及び40°-75%RH条件下に30日間放置する。



表Ⅲ　使用例処方

	実施例 No.	実施例 錠剤(g)	主薬及び賦形剤	しょ糖脂肪酸エステル	計
処方1	2	402g	重炭酸ソーダ 420g	18g	500g
〃2	3	402g	アスコルビン酸 420g	18g	900g
〃3	4	402g	アセチルサリチル酸 420g	18g	900g

表Ⅴ　使用例製剤特性試験

処方No. / 錠剤特性試験項目	処方1	処方2	処方3
錠剤重量平均値	300.5 mg	302.0 mg	301.6 mg
崩壊時間（水）	2.2 分	6.4 分	5.9 分
錠剤20錠の平均モンサント硬度	11.8 kg	13.1 kg	0.1 kg
〃 厚み	3.02 mm	3.34 mm	3.28 mm
錠重偏差	3.22 mg	2.98 mg	3.46 mg

使用例

実施例で得られた試料をアスコルビン酸、重炭酸ソーダ又はアセチルサリチル酸等の主薬と混合し、直接打錠した。

（処方）

実施例2、3又は4で得られた粉末又は顆粒状の試料を表Ⅲ処方に従って主薬と混合し、均一化した。

（打錠条件）

一錠重量が300mgになるよう設定した。HT・P 18型打錠機（畑鉄工所製）を用い、錠剤の直径8mmφ R面の臼杵を組み、2500kg/cm²の圧をかけ、30rpmで打錠した。

（結果）

使用例試験で得られた錠剤についての特性値は下記の通りで、日本薬局方錠剤基準に適合するものであった（表Ⅴ）。

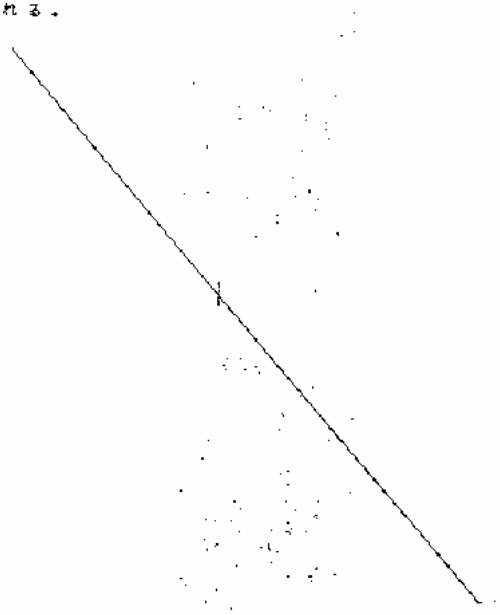
（使用例主薬配合錠剤の直接試験）

使用例処方2の錠剤をアルミのポリキロ包装したものについて40℃恒温下で3ヶ月保存す

る。

（結果）

表Vに示した。主薬含量変化は少ないと思われる。



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表Ⅰから明らかなごとく、本発明の実施例で得られた製品の嵩比容積が1.88～2.36ml/gと低く、安息角が32～38°と良い値を示したほか、吸湿性も低かった。

本発明のある実施例で得られた製品を1,000～3,000kg/cm²の打錠圧で成型したとき、打錠圧の上昇と共に従って硬度も上るが、錠剤成型能が不良のとき起こるキャッピング、クラッキング現象をみることなく（表Ⅱ）、モンサント硬度を5～8kgに調整して錠剤化した試作品は加湿、又は加温・加湿下での虐待条件においても崩壊（Initial）の速い崩壊時間及び硬度は不変であり、モンサント硬度を13～17kgに調整して錠剤化した場合でも、その傾向は変らない（表Ⅲ－1及び表Ⅲ－2）。

又、本発明の各実施例で得られた製品を主薬例えば制酸剤、ビタミン剤又は鎮痛剤の各々と処方し（表Ⅳ）、直接打錠するとき、日本薬局方の錠剤崩壊試験に適合する速い崩壊性を有する錠剤が得られ、又キャッピング等の錠剤成型

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表Ⅴ　虐待試験による使用例製剤の主薬含量変化

処方No. ＼ 項目	条　件	アスコルビン酸含量(%)
処　方　2	Initial	99.2
	40°　3ヶ月	97.2

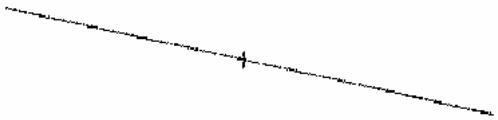
表Ⅵ　X線回折法

実施例	I　比	参考例	I　比
1	0.9	1	——
2	0.7	2	——
3	0.7	3	——
4	1.6	4	——

X線回折法：X線回折装置（理学電機製 RAD-2B型）を用い、Target：Cu、30KV-20mA で測定した。

I比：I_1/I_0

但し、I_0はd値3.33の強度、I_1はd値3.13の強度。又——印はI比が存在しないことを示す。



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土砂ましくない減少もなく、流動性の良好な、しかも製剤重量バラツキの小さな製剤（表Ⅴ）を得ることができた。

ハ）発明の効果

本発明によって得られた製品の流動性、崩壊性、成型性のデーターを、又本発明によって得られた製品と主薬・賦形剤との配合処方した処方の直打製剤品に関する崩壊性、成型性データーを先記した。これを要するに、市販D－マンニトール粉末は成型性が劣いが、でん粉加水分解物の添加量、D－マンニトール及びでん粉加水分解物の膨潤状態、噴霧乾燥条件の要件を加えるとき、直打用賦形剤としての成型性をもったD－マンニトール・でん粉加水分解物複合粉末を得て、得られた粒形は顆粒状粉末から細粒までのみならず、又、成型性も自由に調製できて、本発明から得られた製剤の流動性、崩壊性、成型性特性は既知製剤より好ましいものであって、本発明の製品例えばアスコルビン酸らを用いて実使用した場合でも、上記特性は何等変ら

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ず，崩行試験の結果も好ましい結果を与えた（表Ⅱ）。従って，D－マンニトール・でんぷん加水分解物複合粒子からなる成形物はD－マンニトールの持つ特性に何ら影響を及ぼすことがなく，流動性，崩壊性，成型後の良好な直打用成形物として有用で製剤工程上多大の効果をもたらす。

4　図面の簡単な説明

第1図は本発明の実施例2についての走査型電子顕微鏡写真である。一部が中空球状をなす組織である。第2図は参考例1についての走査型電子顕微鏡写真である。粒状結晶をなしている。又，粒子の大きさを示すため，記載した。

出願人

富士化学工業株式会社

第1図

— 50μm

第2図

— 50μm

手続補正書(方式)

昭和60年　2月13日

特許庁長官　志賀　学　殿

1　事件の表示　昭和59年特許願第203837号

2　発明の名称　直打用成形薬の製造法

3　補正をする者

事件との関係　特許出願人

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代表取締役社長　西田栄正

4　補正命令の日付（発送日）

昭和60年1月29日

5　補正の対象

願書及び明細書の発明の名称の欄

6　補正の内容

別紙のとおり

別紙

1　願書の「1．発明の名称の欄「直打用成形薬の製造法（II）」の（II）を削除し，「直打用成形薬の製造法」とする。

2　明細書第1頁の「1．発明の名称の欄「直打用成形薬の製造法（II）」の（II）を削除し，「直打用成形薬の製造法」とする。

EXHIBIT B

JAPANESE LAID-OPEN PATENT APPLICATION

S61-85330 (1986)

(19) Japan Patent Office (JP)
(11) Publication No. S61-85330
(12) Laid-Open Patent Application (A)
(43) Publication Date April 30, 1986

(51) Int. Cl.[4]	Identification Code	In-House Reference No.
A 61 K 47/00		6742-4C
//A 61 K 9/20		6742-4C

No examination request
Number of claims 1
(totally 6 pages)

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(54) Title of the Invention

PRODUCTION OF EXCIPIENT FOR DIRECT TABLETTING

(21) Application No. PA S59-208636
(22) Date of Filing October 4, 1984 (Showa 59)

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Specification

1. Title of the Invention

Production of Excipient for Direct Tabletting

2. Claims

(1) A production process of excipient for direct tabletting characterized by spray-drying D-mannitol.

(2) The production process of excipient for direct tabletting according to Claim 1 characterized by using an aqueous solution of D-mannitol.

(3) The production process of excipient for direct tabletting according to Claim 1 wherein spray-drying is carried out at an exhaust heat temperature of 120 ~ 140^{o}C.

3. Detailed description of the invention

A) Purpose of the invention

a] Field of industrial Application

The present invention relates to a production process of excipient for direct tabletting. Specifically, the present invention relates to a production process of excipient for direct tabletting characterized by spray-drying D-mannitol and, in the production of primary agents of medicines and base materials of food, relates to a production process of excipient for direct tabletting which consists of water-soluble D-mannitol powder having good fluidity, moldability and disintegrability without exerting any undesirable effects on the primary agents and base materials.

b] Prior art

A commercial D-mannitol has been enjoyed separately as a substitute sweetener in fields of medicine and food industries. However, D-mannitol is rare to be used separately as an excipient, and is frequently formulated with other excipients having good compressibility to obtain

compressed tablets such as troche, chewable tablet, etc. When a water-soluble formulation is obtained with sugars as main body, usually, lactose, etc. are mainly used (*Pharmacia*, **19** (12), 1268 (1983)). Actually other additives such as binder, filler, etc. are blended and used to obtain a formulation with stable form of primary agents. However, the formulation of lactose sometimes causes deficient stability for primary agents of medicines in the former case, and many binders and fillers are insoluble or sparsely soluble in water and therefore water-soluble formulations cannot be obtained in the later case.

c] Problems overcome by the invention

If a water-soluble excipient for direct tabletting which consists of D-mannitol powder having characteristics of D-mannitol, i.e., good pleasantness to palate, cooling sweetness, non-absorption properties, high melting point, improved stability and no blending inhibition with primary agents, improved fluidity, disintegrability and moldability can be obtained, which is preferable in that dispersion of organism utility of primary agents caused by additives of formulation is slight and analysis of formulation can be easily performed.

The inventors considered that the cause of above disadvantage was attributed to the weakness of binding force of the commercial D-mannitol itself, and understood that an augment of the binding force could be achieved by a spray-drying technique, and a desired excipient for direct tabletting could be obtained for the first time by such a production process of D-mannitol having satisfactory moldability as described below, thus they came to accomplish the present invention.

B] Constitution of the invention

a] Problem resolution means

An embodiment of the present invention is based on:

(1) a production process of excipient for direct tabletting characterized by spray-drying D-mannitol.
(2) The production process of excipient for direct tabletting according to Claim 1 wherein an aqueous solution of D-mannitol is used.
(3) The production process of excipient for direct tabletting according to Claim 1 wherein the spraydrying is carried out at an exhaust heat temperature of 120 ~ 140^{o}C.

D-mannitol used in the present invention should be D-mannitol in conformity to *Japanese Pharmacopoeia*, official specifications for food additives, *USP Specifications*, *BP Specifications*, etc. and obtained by any method of a liquid extraction process from marine algae, ammonia electrolytic reduction process of glucose solution and catalytic reduction process of sucrose.

If D-mannitol is spray-dried, the D-mannitol must be completely dissolved. D-mannitol is prepared by completely dissolving it to a concentration of 10 ~ 40 wt/wt%, and the solution is also heated to 60 ~ 80°C at this time.

As spray-drying conditions in a drying step of aqueous solution of D-mannitol at the time of obtaining a D-mannitol powder, if the exhaust heat temperature is selected within a range of 120 ~ 140°C, a desired excipient for direct tabletting with desired moldability, in which the granular form of formulation is fine powder, is obtained. This is because if the D-mannitol powder is dried at 120°C ~ 140°C, the moldability in formulation characteristics of the obtained product relates to the growth and decline of crystals in the X-ray crystallography described later, making it difficult to obtain good products.

b] Efficacy

If an aqueous solution of D-mannitol is spray-dried, fine powders are obtained. A suprising discovery was made by comparing diffraction crystal plane distances d [Å] in the X-ray diffraction method of test products obtained by these products and referential exmples [Table VII]. Namely, it was found that the product obtained from the present invention existed with d values of 5.33 [Å] and 5.15 [Å]; in contrast, the d value of D-mannitol powder was found only at 5.33 [Å], and the d value of test product with poor compression moldability was found only at 5.15 [Å] in reference examples wherein the D-mannitol powder melted until 160°C.

Thus, although a strong correlation was found between good moldability of products obtained in embodiment examples of the present invention and existence with the d values of 5.33 [Å], 5.15 [Å] in the X-ray diffraction method, their working mechanism could not be clarified.

However, in products obtained in the same manner as the embodiment examples of the present invention, fine particle powders give dense filling property and smooth propagating properties of compression depending on dissolved state and spray-drying conditions of D-mannitol

as shown in Fig. 1 of the Drawings, therefore no reduction of characteristics undesirable in formulation, i.e., capping, cracking, are shown.

c] Embodiment examples

Embodiment examples and reference examples for the convenience of understanding the present invention are described below.

Embodiment example 1

10.0 kg of JP (*Japanese Pharmacopoeia*) D-mannitol was added into 30.0 kg of a hot water of 70°C to make a 25.0 w/w% aqueous solution, and it was spray-dried by a rotary disc method at an input heat temperature of 218 ~ 226°C and an exhaust heat temperature of 122 ~ 129°C while maintaining the liquid temperature at 65 ~ 70°C, and 9.36 kg of a fine powder was obtained.

Embodiment example 2

10.0 kg of JP (*Japanese Pharmacopoeia*) D-mannitol was added to 20.0 kg of a hot water of 90°C, was spray-dried by a pressure nozzle method at an input heat temperature of 220 ~ 230°C and an exhaust heat temperature of 130 ~ 131°C while keeping the liquid temperature to 70 ~ 80°C, and 9.5 kg of a fine powder was obtained.

Reference example 1

A 100 mesh through JP D-mannitol powder.

Reference example 2

A JP D-mannitol powder was taken in a ceramic dish, hot melted at about 168°C, cooled and then pulverized, allowed to pass through 30 mesh sieve to sort grains.

Physical property tests and formulation characteristics tests of products obtained by the embodiment examples of the present invention and reference examples were carried out, the results of which are shown in Table I ~ Table III-2. The result obtained by the X-ray diffraction method is shown in Table VI.

Table I Physical properties

Physical property \ Sample		Embodiment example 1	Embodiment example 2	Referential example 1	Referential example 2
Bulk specific volume (mL/g)		1.89	2.01	1.78	1.68
Particle size (%)	32 mesh on	0	0	0	0
	32 ~ 150 mesh	19	36	8	11
	200 mesh through	74	56	84	89
Angle of repose (°)		36	35	44	40
Drying loss[1] (%)		0.02	0.02	0.08	0.02
Hygroscopicity[2]	Moisture absorption (%)	0.01	0.01	0.02	0.03
	Appearance change	none	none	none	none

1) 1.000 g of a sample was accurately weighed in a weighing bottle and dried at 105°C for 3 hr to obtain its loss.

2) A sample was dried at 105°C for 3 hr, about 1.000 g of anhydrous sample was accurately weighed and allowed to stand still at 40°C and 75% RH for 120 hr, then the weight of sample was measured, and a weight gain was moisture absorption. Appearance changes at this time were also observed at the same time.

Table II Formulation characteristic test: compression moldability

Tabletting pressure \ Sample	Embodiment example 1	Embodiment example 2	Referential example 1	Referential example 2
1,000 kg/cm^2	5.3	5.8	3.2	Capping occurs and molding is impossible
2,000 kg/cm^2	10.4	9.9	Capping occurs and molding is impossible	Capping occurs and molding is impossible
3,000 kg/cm^2	13.2	13.4	Capping occurs and molding is impossible	Capping occurs and molding is impossible

Numerical values in table are Monsanto hardness (kg)

Tabletting conditions:

1% of magnesium stearate was added to each sample, and static compression tabletting was carried out at a setting of 300 mg per tablet by a Brinell hardness tester (made by Yonekura Co., Ltd.) with a 10 mmϕ parallel pestle.

1. Hardness of tablets

20 tablets are measured, respectively by a Monsanto hardness meter and the hardness is obtained in their average value.

2. Thickness of tablets

20 tablets are measured, respectively by a micrometer and the thickness is obtained in their average value.

3. Disintegration test

An average time measured according to a disintegration test method of *Japanese Pharma-copoeia*. However, an auxiliary disk is not used.

4. Weight of formulation

20 tablets are measured, respectively and the weight is obtained in their average value.

Table III-1 Formulation characteristics test: changes of formulation characteristics by maltreatment test (when prepared into tablet hardness 5 ~ 6 kg)

Sample		Embodiment example 1	Embodiment example 2	Referential example 1	Referential example 2
Tabletting pressure (kg/cm^2)		1,500	1,500	1,500	-
Characteristic value of tablet / Maltreatment conditions					
Thickness (mm)	Initial	3.08	3.07	3.03	Capping occurs and molding is impossible
	40°C	3.08	3.07	3.03	
	40°C≧75% RH	3.08	3.07	3.03	
Monsanto hardness (kg)	Initial	5.3	5.8	5.5	
	40°C	5.4	5.9	5.6	
	40°C≧75% RH	5.4	5.8	5.8	
Disintegration time (min)	Initial	0.7	0.8	1.8	
	40°C	0.8	0.9	1.6	
	40°C≧75% RH	0.9	0.9	2.0	
Weight (mg)	Initial	300	301	300	
	40°C	300	301	300	
	40°C≧75% RH	300	301	300	

Table III-2 Formulation characteristics test: changes of formulation characteristics by maltreatment test (when prepared into tablet hardness 9 ~ 10 kg)

Sample		Embodiment example 1	Embodiment example 2	Referential example 1	Referential example 2
Tabletting pressure (kg/cm^2)		2,000	2,000	-	-
Characteristic value of tablet / Maltreatment conditions					
Thickness (mm)	Initial	2.76	2.78	Capping occurs and molding is impossible	
	40°C	2.76	2.78		
	40°C≅75% RH	2.76	2.78		
Monsanto hardness (kg)	Initial	10.4	9.9		
	40°C	10.5	10.0		
	40°C≅75% RH	10.4	10.0		
Disintegration time (min)	Initial	1.9	2.0		
	40°C	2.1	1.9		
	40°C≅75% RH	2.0	1.9		
Weight (mg)	Initial	302	301		
	40°C	302	301		
	40°C≅75% RH	302	301		

In the maltreatment tests, tablets of each sample were packaged with 7 μ N_Ξ>[and maltreated for 30 days under conditions 40°C and 40°C≅75% RH.

Table IV Formulas for application examples

	Sample of embodiment example of present invention		Amounts of main agent and sample	Magnesium stearate	Total
	No.	Amount of sample			
Formula 1	1	975 g	Diazepam 20 g	5 g	1,000 g
Formula 2	2	970 g	Thiamine sulfide 25 g	5 g	1,000 g

Table V Formulation characteristics test for application examples

Formula No. Test items of tablet characteristics	Formula 1	Formula 2
Weight-average value of tablets	101.2 mg	102.1 mg
Disintegration time (min)	3.8 min	3.0 min
Average Monsanto hardness of 20 tablets	5.0 kg	4.8 kg
Average thickness of 20 tablets	3.07 mm	3.13 mm
Standard deviation	1.33 mg	1.68 mg

Application examples

The samples obtained in Embodiment examples 1, 2 were mixed with the primary agents diazepam and thiamine sulfide by a factor and then directly tabletted.

<Formulas>

The samples obtained in Embodiment examples 1, 2 were mixed with the primary agents according to Table IV and then homogenized.

<Tabletting conditions>

The weight per tablet was set to become 100 mg. The sample was tabletted at 25 rpm by assembling an R-type pestle of 6 mm ϕ in tablet diameter and applying a pressure of 2,000 kg/cm^2 using an HT-P18 tabletting machine (made by Hada Iron Works).

<Results>

Characteristic values of tablets obtained by the application examples are as Table 5, and they were in conformity with the standard for JP tablets (Table V).

Table VI X-ray diffraction method

	I ratio
Embodiment example 1	4.1
Embodiment example 2	3.9
Reference example 1	no
Reference example 2	no

X-ray diffraction method: The samples were measured with a target: Cu at 30 KV-20 mA by an X-ray diffractometer (RAD-20 IA, made by Rigaku Denki Co., Ltd.).

I ratio: I_1/I_0

However, I_0 is the intensity at a d value of 5.33, and I_1 is the intensity at a d value of 5.15.

As is evident from Table I, the bulk specific volume of products obtained by embodiment examples of the present invention is as low as 1.88 ~ 2.01 mL/g, the angle of repose showed a value as good as 35 ~ 36°, and the hygroscopicity was also low.

When the products obtained by embodiment examples of the present invention are molded at a tabletting pressure of 1,000 ~ 3,000 kg/cm^2, the hardness also rises with a rise of tabletting pressure, but capping, cracking phenomena occurring in case of poor tabletting moldabilty are not observed (Table II), the initial rapid disintegration time and hardness of trial products formulated by adjusting the Monsanto hardness to 5 ~ 6 kg are unchanged even under the maltreatment conditions of heating and moistening, and this tendency is not changed even if the products are formulated by adjusting the Monsanto hardness to 9 ~ 11 kg (Table III-1 and Table III-2).

C) Efficacy of the invention

The data of fluidity and moldability of products obtained by the present invention were des-cribed above. In short, although the commercial D-mannitol powder has no moldability, when the invention is carried out by satisfying the dissolved state and spray-dried state of D-mannitol, the invented D-mannitol gives an excipient for direct tabletting which consists of D-mannitol powder with certainly good moldability and good fluidity and disintegrability, therefore the present invention is useful and brings a great effect in the formulation process.

4. Brief description of the drawings

Fig. 1 is a scanning electron micrograph of Embodiment example 1 of the present invention. It is a powder with nearly spherical fine grains. Fig. 2 is a scanning electron micrograph of Reference example 1. It forms columnar crystals. The grain sizes are noted.

Fig. 1

Fig. 2

⑲日本国特許庁（JP）　⑪特許出願公開

⑫公開特許公報（A）　昭61－85330

⑤Int.Cl.⁴	識別記号	庁内整理番号	⑬公開　昭和61年(1986)4月30日
A 61 K 47/00		6742－4C	
// A 61 K 9/20		6742－4C	

審査請求　未請求　発明の数 1　（全6頁）

⑭発明の名称　直打用賦形薬の製造法

⑳特　願　昭59－208636
㉒出　願　昭59(1984)10月4日

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明　細　書

1．発明の名称

直打用賦形薬の製造法（1）

2．特許請求の範囲

(1) D－マンニトールを噴霧乾燥することを特長とする直打用賦形薬の製造法。

(2) D－マンニトールの水溶液を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法。

(3) 噴霧乾燥を排熱温度 120～140 ℃で行う特許請求の範囲第1項記載の直打用賦形薬の製造法。

3．発明の詳細な説明

(1) 発明の目的

A] 産業上の利用分野

本発明は直打用賦形薬の製造法に関するものである。更に詳しくは、D－マンニトールを噴霧乾燥することを特長とする直打用賦形薬の製造法に関するものであって、産業上医薬品の主薬、食品の主材の製剤化に際して、それら主薬、主材に何等の好ましからざる作用を及ぼすことなく、流動性、成型性、崩壊性の良い水可溶性のD－マンニトール製剤よりなる直打用賦形薬の製造法に関するものである。

B] 従来の技術

市販D－マンニトールは代替甘味料として単独で医薬品、食品産業分野において使用されている。然しながら、賦形剤として用いる場合、D－マンニトール単独では使用されることは少なく、例えばトローチ、チュアブル錠等の圧縮錠を得るには、圧縮性の良い他の賦形薬と配合して用いられることが多い。糖類を主体にして水可溶形の錠剤を得ようとする場合、通常主として乳糖等が用いられ（ファルマシア，18(12) 1268(1982)）、又、主薬安定形の錠剤を得るには、結合剤、フィラーなど他の添加物を配合して用いられているのが実情である。然しながら、前者にあっては乳糖配合が原因して、医薬品の主薬に対して安定性を欠く場合があり、後

合の場合には結合剤，フィラーの多くは水不溶性又は難溶性のものであるため，水可溶性製剤を得ることができない欠点がある。

c] 発明が解決しようとする問題点

D－マンニトールの持つ特性，即ち苦みやえぐみの少ない涼しい口当り，非吸湿性，高融点，良好な安定性，主薬との配合禁忌がない等の性質に何等悪影響を及ぼすことがなく，流動性，崩壊性，成型性の良好なD－マンニトール粉末よりなる水可溶性の直打用賦形薬が得られれば，製剤経過物に起因する主薬の生体利用率のバラツキが少なく，又製剤分析を容易に行える点でも好ましいと考える。

本発明者らは上記の欠点の根源は市販のD－マンニトール自身の結合力の弱さに起因すると考え，その結合力の増強を噴霧乾燥法等によってはかり，満足すべき成型性をもするD－マンニトールを，次に述べるような製造法によって初めて所望の直打用賦形薬を得ることが出来ることを知り，本発明を完成するに至った。

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D－マンニトール粉末を得るに際してのD－マンニトール水溶液の乾燥工程における噴霧乾燥条件としては，熱風温度 120～140 ℃の範囲を選べば，製剤の粒形は新規形状である顕著する成型性の良好な直打用賦形薬が得られる。120 ℃以下あるいは 140℃以上で乾燥すれば，得られる製品の製剤特性のうち成型性が低下する又結晶粉末中の結晶の割合に関係するので，良好な製品を得ることは困難であるからである。

D] 作用

D－マンニトールの水溶液を噴霧乾燥すれば，顕微状粉末が得られる。これら製品と参考例で得られた市販品の X 線回折法における面間隔 d [Å] を比較して驚くべき発見をした［表四］。即ち，本発明から得られた製品は d 値が 5.33 [Å] と 5.15 [Å] を持って存在することを認めるのに対し，D－マンニトール粉末及び d 値が 5.33 [Å] にのみ認めるにすぎず，又D－マンニトール粉末の 160℃まで溶融

5

E] 発明の構成

A] 問題点を解決するための手段

実施態様で示せば，(1) D－マンニトールを噴霧乾燥することを特徴とする直打用賦形薬の製造法，(2) D－マンニトールの水溶液を用いる特許請求の範囲第1項記載の直打用賦形薬の製造法，(3) 噴霧乾燥を排熱温度 120～140 ℃で行う特許請求の範囲第1項記載の直打用賦形薬の製造法によるものである。

本発明に用いられるD－マンニトールは海藻からの抽出精製法，ぶどう糖液のアンモニア還元法，しょ糖溶液の接触還元法のいずれかの方法によって得られた日本薬局方，食品添加物公定書規格，USP 規格，BP 規格に適するD－マンニトールであればよい。

D－マンニトールを噴霧乾燥する際，D－マンニトールを完溶させることが要求される。又，その濃度は 10～40重量／重量%に至るまで調製されるが，このとき 80～90℃に加温することもある。

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を行った参考例の圧縮成型物の本発明な試験面は d 値が 5.15 [Å] にのみ認めるにしかすぎない。

このように，本発明の実施例で得られた製品が成型性の良好な特徴を有することと，又顕微新規において d 値が 5.33 [Å]，5.15 [Å] に伴って存在することを認めることとの間に深い相関性を見出したにも関わらず，それらが作用機序をここで明らかにすることはできなかった。

然しながらいずれにしても，本発明の実施例のごとくにして得られた製品は，D－マンニトールの溶解状態，噴霧乾燥条件により，「発明の詳細な説明」の第1図に示すように，顕微状粉末が流れ性と圧縮の円滑な伝播性を有するが故に，製剤上好ましくない特性，即ちキャッピング，クラッキング減少を示すことはないものとみえれる。

C] 実施例

以下に本発明についての理解を助ならしめる

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ための実施例、参考例を記す。

実施例1

日局Dマンニトール10.0kgを70℃の温湯30.0kgに加え、25.0w/w%水溶液となし、液温を65～70℃に保持しながら、入熱温度 218～228 ℃、排熱温度 122～128 ℃で回転円板法にて噴霧乾燥を行い、9.36kgの細粒状粉末を得た。

実施例2

日局Dマンニトール10.0kgを80℃の温湯29kgに加え、液温を70～80℃に保持しながら、入熱温度 220～230 ℃、排熱温度 130～101 ℃で加圧ノズル法にて噴霧乾燥を行い、9.5kgの細粒状粉末を得た。

参考例1

日局Dマンニトールの100メッシュ通過物。

参考例2

日局Dマンニトールを蒸発皿に取り、約188 ℃に加熱溶融させ、冷却固化し、80メッシュ通過物とした。

表I 物性値

物性 ＼ 試料		実施例1	実施例2	参考例1	参考例2
嵩比容 (ml/g)		1.89	2.01	1.78	1.68
粒度(%)	32 mesh on	0	0	0	0
	32-150 mesh	19	36	8	11
	250 mesh th	74	56	84	89
安息角 (°)		36	35	44	40
乾燥減量[1] (%)		0.02	0.02	0.06	0.02
吸湿性[2]	吸湿率 (%)	0.01	0.01	0.02	0.03
	外観変化	なし	なし	なし	なし

1) 秤量瓶に試料1.000gを正確に取り、105°・3時間乾燥し、その減量を求める。

2) 試料を105°・3時間乾燥し、恒水物としたもの約1.000gを正確に取り、40°・75%RH下に120時間静置した後、試料重量を測定し重量の増加分を吸湿量とする。又、このときの外観変化についても同時に観察する。

表II 錠剤特性試験：圧縮成型性

試料 ＼ 打錠圧	実施例1	実施例2	参考例1	参考例2
1,000 kg/cm²	5.3	5.8	3.2	キャッピングが生じ成型不可能
2,000 kg/cm²	10.4	9.9	キャッピングが生じ成型不可能	キャッピングが生じ成型不可能
3,000 kg/cm²	13.2	13.4	キャッピングが生じ成型不可能	キャッピングが生じ成型不可能

錠剤の数値はモンサント硬度 (kg)

打錠条件：

各試料にステアリン酸マグネシウムを1部加し、10mmφ平杵を用い、1錠300mgの設定で、プリネル硬さ試験機（木屋製作所製）を用い、静的圧縮打錠を行う。

錠剤の特性試験方法：

1.錠剤の硬度

モンサント硬度計を用い、20錠について各々測定し、平均値で求める。

2.錠剤の厚み

マイクロメーターを用い、20錠について各々測定し、平均値で求める。

3.崩壊試験

日本薬局方の崩壊試験法に準じて測定した平均時間。但し、補助盤は用いない。

4.錠剤の脆損

20錠について各々測定し、その平均値で求める。

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表Ⅰ－1　錠剤特性試験：連打試験による錠剤特性の変化
（錠剤硬度5～6kgに調製した場合）

錠剤特性値 ＼ 試料		実施例1	実施例2	参考例1	参考例2
	打錠圧 (kg/cm²)	1,500	1,500	1,500	——
	連打条件				
厚み (mm)	Initial	3.08	3.09	3.08	キャッピングが生じ成型不可能
	40°	3.08	3.07	3.08	
	40°・75%RH	3.06	3.07	3.08	
モンサント硬度 (kg)	Initial	5.2	5.8	5.5	
	40°	5.4	5.9	5.6	
	40°・75%RH	5.4	5.8	5.8	
崩壊時間 (分)	Initial	0.7	0.8	1.8	
	40°	0.8	0.9	1.5	
	40°・75%RH	0.8	0.9	2.0	
質量 (mg)	Initial	300	301	300	
	40°	300	301	300	
	40°・75%RH	300	301	300	

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表Ⅰ－2　錠剤特性試験：連打試験による錠剤特性の変化
（錠剤硬度8～10kgに調製した場合）

錠剤特性値 ＼ 試料		実施例1	実施例2	参考例1	参考例2
	打錠圧 (kg/cm²)	2,000	2,000	——	——
	連打条件				
厚み (mm)	Initial	2.78	2.76	キャッピングが生じ成型不可能	
	40°	2.78	2.78		
	40°・75%RH	2.78	2.79		
モンサント硬度 (kg)	Initial	10.4	8.8		
	40°	10.5	10.0		
	40°・75%RH	10.4	10.0		
崩壊時間 (分)	Initial	1.8	2.0		
	40°	2.1	1.9		
	40°・75%RH	2.0	1.8		
重量 (mg)	Initial	302	301		
	40°	302	301		
	40°・75%RH	302	301		

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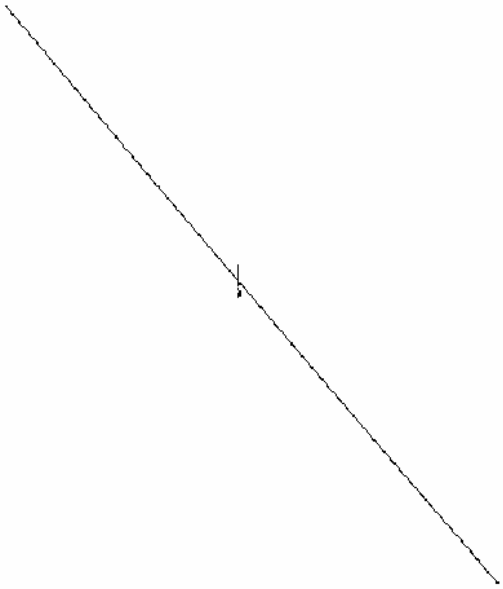
安定試験は、各試料の錠剤をアルミピロ包装し、40°及び40°・75%RH条件下に3ヶ月間保存する。



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表IV 使用例処方

	本発明の実施例の造粒物 No.	造粒物	主薬及び試料量	ステアリン酸マグネシウム	計
処方1	1	975g	ジアゼパム 20g	5g	1000g
処方2	2	970g	チアミンスルフィード 25g	5g	1000g

表V 使用例錠剤物性試験

錠剤物性試験項目 処方No.	処方1	処方2
錠剤重量平均値	101.2 mg	102.1 mg
崩壊時間（水）	3.6 分	3.0 分
錠剤20錠の平均モンサント硬度	5.0 kg	4.8 kg
〃 厚み	3.07 mm	3.13 mm
標準偏差	1.38 mg	1.66 mg

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表VI X線回析法

	I 比
実施例1	4.1
実施例2	3.9
参考例1	なし
参考例2	なし

X線回析法：X線回析装置（理学電機製 RAD-2CA型）を用い、Target：Cu，30KV-20mA で測定した。

I比：I_1/I_2

但し、I_1は d値 5.33の強度，I_2は d値 5.15の強度

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（表の続き）

錠剤例

実施例1、2で得られた試料をジアゼパム、チアミンスルフィードの主薬と混合し、直接打錠した。

（処方）

実施例1、2で得られた粉末の試料を表IV処方に従って主薬と混合し、均一化した。

（打錠条件）

一錠重量が 100mgになるよう設定した。RT・P18型打錠機（畑鉄工所製）を用い、錠剤の直径 8mmφR型の臼杵を用み、2000kg/cm²の圧をかけ、25rpm で打錠した。

（結果）

使用例試験で得られた錠剤についての物性値は表Vの通りで、日本薬局方錠剤規格に適合するものであった（表V）。

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表Iから明らかなごとく、本発明の実施例で得られた製品の嵩比容積が1.83～2.01ml/gと高く、安息角が35～38°と良い値を示したほか、吸湿性も低かった。

本発明の各実施例で得られた製品を1,000～3,000kg/cm²の打錠圧で成形したとき、打錠圧の上昇と共に硬度も上るが、錠剤成形機が不良のとき起こるキャッピング、クラッキング現象をみることなく（表II）、モンサント硬度を 5～8kg に調整して製剤化した試作品は加湿、又は加温・加湿下での崩壊条件においても初期（Initial）の速い崩壊時間及び硬度は不変であり、モンサント硬度を 3～11kgに調整して製剤化した場合でも、その傾向は変らない（表III－1及び表III－2）。

（ヘ）発明の効果

本発明によって得られた製品の流動性、成型性のデーターを先記した。これを要するに崩壊D－マンニトール粉末は成型剤がなくが、本発明の、D－マンニトールの溶解状態及び噴霧乾

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効果を充し実施されるとき，成型性能は勿論，流動性，制振性の良好なD－マンニトール結晶よりなる直打用賦形薬を与えるので，有用であり，製剤工程上多大の効果をもたらす。

4　図面の簡単な説明

第1図は本発明の実施例1についての走査型電子顕微鏡写真である。球状に近い細粒状粉末である。第2図は参考例1についての走査型電子顕微鏡写真である。非状結晶をなしている。又，括弧の大きさを示すため註記した。

出願人

富士化学工業株式会社

第1図

第2図

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手　続　補　正　書（方式）

昭和60年　2月13日

特許庁長官　志　賀　　学　殿

1　事件の表示　昭和59年特許願第208636号

2　発明の名称　直打用賦形薬の製造法

3　補正をする者

事件との関係　特許出願人

住　所　富山県中新川郡[illegible]町(横法音寺)55番地

氏　名　富士化学[illegible]株式会社

代表取締役社長　[illegible]

4　補正命令の日付（発送日）

昭和60年1月29日

5　補正の対象

願書及び明細書の発明の名称の欄

6　補正の内容

別紙のとおり

別紙

1　願書の「1．発明の名称の欄「直打用賦形薬の製造法（Ⅰ）」の（Ⅰ）を削除し、「直打用賦形薬の製造法」とする。

2　明細書第1頁の「1．発明の名称の欄「直打用賦形薬の製造法（Ⅰ）」の（Ⅰ）を削除し、「直打用賦形薬の製造法」とする。

EXHIBIT C

(19) Japan Patent Office (JP) (11) Patent Application Publication

(12) Patent Publication (B2) **S55-36646**

(51) Int. Cl.[3]	ID Code	Internal Classification No.	(24) (44) Publication: September 22, 1980
C 07 C 31/18		6742-4H	
29/00			

Number of inventions: 1

(Altogether 4 pages)

(54) A manufacturing method of granular powder of crystalline sugar alcohol.

(21) Pat App: S51-139716

(22) Application: November 19, 1976

Laid-Open: S53-65806

(43) June 12, 1978

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(56) Citation:

Patent Publication S49-41169 (JP, B1)

(57) Scope of Patent Claims

1. A manufacturing method of granular powder of crystalline sugar alcohol, wherein sugar alcohol powder is mixed in a nearly-oversaturated crystalline sugar alcohol solution in an amount that can create sugar alcohol powder in the amount of about 20 % or more in said solution, wherein the viscosity of said solution is lowered by maturing it in a state where undissolved powder sugar alcohol coexists, and it is spray-dried.

2. The manufacturing method described in Scope of Patent Claims 1, wherein desired materials are further mixed in with crystalline sugar alcohol.

Detailed Explanation of the Invention

The present invention relates to a manufacturing method of granular powder of crystalline sugar alcohol.

Whereas crystalline sugar alcohols such as sorbitol, mannitol, and inositol have a wide variety of applications whether in the food or non-food field, and their demand has been increasing in recent years, their powder form which is easy to handle, especially granular powder, is not known so far.

Whereas some powdering methods of said sugar alcohols, such as so-called the block solidification and pulverization method and the granulation method are publicly known, because these methods do not necessarily consider high solubility and crystallization specificity of crystalline sugar alcohols sufficiently, they have had serious difficulties with the physical properties of products such as workability and moisture resistance.

Said situation is explained in greater details for sorbitol as an example.

① Block solidification and pulverization method

A sorbitol solution is condensed to 90 % or higher, having seed crystals added, and is stirred and dispersed into a box-shape container, an opal-looking solidified mass is removed from the container after several hours, these are piled over one another to wait for cooling and internal solidification over a long time, pulverized or cut, dried, and sieved to make it a product.

② Granulation method

A sorbitol condensed solution is jetted onto a relatively large amount of crystalline sorbitol powder which is made fluid, the sorbitol condensed solution is held in the interstices of multiple particles of the crystalline sorbitol powder, it is pulverized after it is solidified, and a part of it is used as a product and the rest is recycled.

In said solidification method ①, because much mass needs to be stored and processed, its labor productivity is low, and because its manufacturing process consists of many stages, management is not easy. Further, in pulverizing solidified sorbit masses, solution part remaining inside each mass becomes exposed on each broken face by pulverization, which causes stickiness and thus caking of the powder, with serious practical shortcomings.

Also, said granulation method ② is based on a mechanism that dries powder and liquid by making them contact and connect with each other. In this granulation method, as the amount of liquid is increases relative to the amount of powder, the amount of powder particles which stick/are caught by liquid particles increases. Furthermore the secondary and higher order coagulations of those wet aggregate particles increase according to the amount of added liquid, and in an extreme case all of the powder in the apparatus becomes one mass, which makes the operation impossible, making it necessary to evenly disperse a relatively small amount of liquid in the presence of a relatively large amount of powder.

In the case of sugar alcohols such as sorbitol, in powdering by such granulation method as this, the condensed solution jetted onto powder must be no more than 1/3 ~ 1/4 (dry ratio) of the amount of powder. This means that 2/3 ~ 3/4 of the amount of powder is repeatedly recycled, and not only the apparatus efficiency must be made 1/3 ~ 1/4, but also the hot air contact average time must be tripled ~ quadrupled. Because the granulated particles always grow to become as large as several times the particle diameter, they must be processed by a grinder. Yet, the powder obtained in such a manner does not have granular particles but just particles of indefinite shape made by pulverizing a larger mass.

On the other hand, granular particles have the advantage that they do not solidify in storage, are easy to dissolve, and can be continuously manufactured, thus having a high labor productivity and a fluidity that enables the obtained product to be continuously mechanically filled into containers. However, such granular powder cannot be obtained by said publicly-known method. While it is known that glucose is powdered by the spray-dry method (Japanese

Patent Publication S39-4834), the spray-dry method of glucose cannot be applied to powdering crystalline sugar alcohols in its existent state.

The reason for this is that while glucose by nature has the property of being easily crystallized, although sugar alcohols have crystallinity, its crystallinity is far smaller, and no powder can be obtained by the powdering method of glucose.

In order to powder sugar alcohols which have such a specific property, the present inventors solved the problem by implementing a special means as a result of their research and completed the present invention.

In the present invention, while the concentration of a sugar alcohol solution does not need to be oversaturated, powder sugar alcohol is added to the solution, which must then be matured in the presence of powder. Then, the spray-dry method is used as its drying means.

Therefore, if the concentration of the sugar alcohol solution is low, a large amount of sugar alcohol powder needs to be added, and it is preferred that the sugar alcohol solution is pre-condensed, and if possible oversaturated, to obtain a good result.

Next, maturation after adding powder sugar alcohols is one of essential points of the present invention, and without going through the maturation process, spray-drying is impossible. In other words, the viscosity of the solution decreases during the maturation, which can make spraying and granule formation smooth. The phenomenon of a viscosity decrease during maturation is a special phenomenon which is seen only in sugar alcohols. In view of the fact that viscosity increases in glucose, conversely, it is a special property proprietary to sugar alcohols which could not be predicted.

In the above manner, it is understood that powdering sugar alcohols and powdering glucose are completely different in terms of their technical content.

The concentration of the solution, powder addition, and maturation are all commonly necessary in powdering sugar alcohols, the amount of powder in presence, maturation time, and viscosity at the time of spray-drying depend somewhat on the kind of sugar alcohol.

For example, when using sorbiol, if maturation is performed 15~24 hours at 25~50 °C in the presence of 25~45 % of powder sorbitol in a sorbitol solution, a preferable result is obtained. Viscosity in spray-drying after maturation should be 2000~50000 cps.

Other than this, in the case of xylitol for example, if maturation is performed 15~24 hours at 25~50 °C in the presence of 20~40 % of xylitol powder in a xylitol solution, a preferable result is obtained. Viscosity in spray-drying after this should be 1000~5000 cps.

Cases with other sugar alcohols are mostly similar to the above.

The present invention is explained in detail with sorbitol which is a representative material of sugar alcohols as an example.

Sorbitol has an extremely strong hydrophily and thus hygroscopicity, 100 g of sorbitol absorbs 50 g of water and completely comes into a solution state at a temperature of 26.7 °C and a relative humidity (R, H) of 80 %, and the solubility of pure sorbitol is about 70 % at 20 °C and about 74 % at 30 °C, showing a moderate solubility slope.

(Other sugar alcohols have nearly the same property.)

In order to prepare sorbitol having such a solubility property in a musket shape, crystallization from a highly-condensed solution needs to be performed. However, if a small amount of seed is mixed in a solution of 80 % or higher and it is left alone, gelation of the entire condensed solution occurs before the growth of the crystal grains occurs, and transitioning to needle-like crystals is delayed.

In this case, if said crystallization work is performed while stirring with a powerful machine such as a kneader, the entire solution becomes solidified, and even stirring becomes impossible.

For reference, if a solution of crystalline sugar alcohols such as sorbitol is spray-dried as it is, dried fine powder is obtained. However, it is a sugar alcohol solution which has become extremely dehydrated, in other words a solidified solution or a solid solution having no crystallinity. Whereas it appears to be a transparent glass spherule under a microscope, once it is exposed to the outside atmosphere, it immediately absorbs moisture, loses fluidity due to intergranular cementation of the powder, and eventually the whole becomes one mass, losing its powdery property.

In this way, a stable sugar alcohol powder cannot be obtained by just spray-drying a sugar alcohol solution.

If a relatively large amount of crystalline powder is mixed in a sorbitol solution of about 80 % concentration, a normal maturation process of the sorbitol solution is seen without going through gelation of the whole solution, its viscosity decreases, and a musket which is easy to spray-dry can be prepared with a solution such as sorbitol, making available a spray-dry method which is an extremely industrially advantageous dry powdering method.

In spray-drying the sorbitol musket, it is theoretically preferable that the condensed sorbitol solution contained in dry particles leaves some isolated water and in a state that allows crystal growth, and it is believed to be necessary that the condensed solution be contained inside aggregations of crystals. According to experiments, while the work is not impossible if 20 % or more crystalline sorbitol exists in a sorbitol musket, it becomes evident that the presence of 30 % or more of crystalline sorbitol is preferred in order to discharge dried powder smoothly and in a short time and obtain a stable product.

The form of musket-shape sorbitol immediately after spray-drying is a form wherein condensed sorbitol solution is contained in aggregates of crystals contained in the musket, which react sensitively to temperature, the particles are softened by warm wind, and the entire body becomes a high-viscosity fluid mass at an even higher temperature. Therefore, the air-exhaust temperature of the dryer needs to be selected considering the thermal properties such as melting point and softening point of sorbitol.

The powder thus obtained is referred to as granules, a group of shiny spherical particles which are usually aggregates of needle crystals, seen under a microscope.

Although the above explanation was given with sorbitol as an example, the same is true for other sugar alcohols such as mannitol, inositol, and xylitol.

Also it is easy to manufacture crystalline sugar alcohol granular powder, wherein water-soluble materials such as sugars, synthetic sweetener, coloring agent, medicine, and organic acid are intimately mixed, and/or water-insoluble materials such as perfume, fat, pigment, and medicine are mixed as fine powder into such a musket and/or solution before preparing a musket, and dried by a method such as the spray-drying method, so that those additives are equally contained in the dried fine powder particles.

Other materials to mix need to be those which do not cause any problem in implementing the present invention, added by appropriate amount, and do not have any bad influence on the quality such as moisture-resistance stability of the obtained product.

Therefore, it could be understood that the present invention also provides a manufacturing method of a mixed powder consisting of crystalline sugar alcohols and other useful materials.

As explained above, the present invention has achieved significant progresses in manufacturing granular powders of crystalline sugar alcohols such as sorbitol having high solubility and crystallization specificity in that it has succeeded in providing a new method of easy and highly-efficient industrial production, and that the quality of the obtained products is such that they are mainly made of sugar alcohol crystals, highly superior in moisture-resistance stability, and rich in powder fluidity.

Next, the present invention is explained referring to its embodiments.

Embodiment 1

In a crystallizer with a jacket, 5 kg of 75 % sorbitol solution was placed, stirred, and prepared to remain at 30 °C in temperature. Meanwhile, when 1.25 kg of crystalline powder of sorbitol was added little by little to said solution and evenly dispersed, and stirring was continued, it became creamy in about 3 hours, in which stage the viscosity was so high that pumping was impossible. When stirring was further continued, due to the decrease in concentration of the solution side along with crystallization, viscosity gradually decreased, dropped to 30000 cps / 30 °C in 20 hours.

The musket-shape sorbitol obtained in this manner was spray-dried to obtain sorbitol powder. Almost no softening-cementing on the internal surface of the dryer was seen at the air-blowing temperature of 65 °C.

By just leaving a dried power alone, crystallization inside particles progresses, increasing the particle hardness and moisture-resistance stability. If a product containing a lower amount of water is desired, using a rotary drier or a fluidized-bed dryer, a product containing water by 2 % or lower can be obtained in a short time. In this stage, sorbitol powder can stand dry hot air of 70~80 °C.

When observed under a microscope, it turns out to be shiny granular powder, consisting of transparent needle-crystals.

Embodiment 2

In a crystallizer with a jacket, 5 kg of 77 % sorbitol solution was placed, while stirring it at 30 °C, 0.75 kg of the crystalline powder sorbitol obtained in Embodiment 1 was added little by little to said solution to make it a homogeneous creamy colloid, stirring was continued at the same temperature, and 24 hours later it was spray-dried in the same condition as Embodiment 1, obtaining crystalline granular sorbitol powder.

Embodiment 3

In a crystallizer with a jacket, 5 kg of 82 % sorbitol solution was placed, it was prepared to remain at 45 °C in temperature while stirring, 1 kg of the crystalline granular sorbitol obtained earlier was added gradually to make it a homogeneous creamy colloid, stirring was continued at 45 °C, a musket-shape sorbitol was obtained 24 hours later, and granular sorbitol powder was obtained by spray-drying it in the same condition as Embodiments 1 and 2.

Embodiment 4

In the same way as in Embodiment 1, 5 kg of 75 % xylitol solution was stirred at 30 °C in a crystallizer, 0.75 kg of powder xylitol was added little by little to said solution to make it a homogeneous creamy colloid, it was stirred at the same temperature 15 hours and spray-dried in the same condition as the above at 3000 cps viscosity, obtaining crystalline granular xylitol. Its appearance in microscopic examination was extremely similar to the products obtained in Embodiments 1, 2, and 3, and its moisture-resistance stability, powder fluidity, and so on were good.

Embodiment 5

As in Embodiment 1, 5 kg of 75 % sorbitol solution was stirred at 30 °C in a crystallizer, 29 g of stevioside powder was dissolved in a small amount of water and added to this, intimately mixed, crystalline powder sorbitol was added little by little to this to make it homogeneous and creamy, stirred at 30 °C for 24 hours, and continued to obtain a musket-shape sorbitol with stevioside homogeneously dissolved. This was spray-dried in the same way as in Embodiment 1, obtaining crystalline granular powder similar to the above, having an equivalent sweet flavor to sugar.

Comparison 1

Whereas crystalline powder sorbitol was spray-dried with no additive in the same condition as in Embodiment 1, the powder accumulated on the interior wall of the dryer and could not be discharged. When a part of it was taken and examined under a microscope, it was confirmed that it consisted of colorless, transparent, spherical particles. These particles absorbed moisture and adhered onto a glass plate in the outside air.

Comparison 2

Crystalline powder sorbitol 150 g was added to 5 kg of a sorbitol solution of 80 % concentration, it was stirred at 30 °C in a crystallizer with a jacket, and musket preparation was attempted. However, it became an opal-color gel 30 minutes later, next solidified and had no change seen over a long time. In other words, it could not be made into a powder.

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1

⑤4結晶性糖アルコールの顆粒状粉末の製法

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⑤特許請求の範囲

1　ほぼ過飽和状態の結晶性糖アルコール溶液に、該溶液中約20%以上の糖アルコール粉末を存在せしめ得る量の前記糖アルコールの粉末を混合し、溶解しない粉末状の糖アルコールが存在する状態で前記溶液の熟成を行うことにより溶液の粘度を低下せしめ、ついで噴霧乾燥することを特徴とする結晶性糖アルコールの顆粒状粉末の製法。

2　前記結晶性糖アルコール溶液に更に所望の物質を混和することを特徴とする特許請求の範囲第1項に記載の製法。

発明の詳細な説明

本発明は、結晶性糖アルコールの顆粒状粉末製法に係る。

ソルビトール、マンニトール、イノシトール等の結晶性糖アルコールは、食品、非食品の分野を問わず極めて広汎な用途を有し、その需要は近時増大しつつあるが、取扱いに便利な粉末、特に顆粒状粉末は従来知られていない。

上記糖アルコールの粉末化法としては、所謂ブロック固化粉砕法、造粒法等が公知であるが、これらの方法は結晶性糖アルコールの高溶解性や、晶出特異性などを必ずしも充分に考慮したものではないため、作業性或いは耐湿性などの製品の物性の点で重大な困難を有するものであつた。

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以下ソルビトールを例にとり上記の事情をより詳細に説明する。

①　ブロック固化粉砕法

ソルビトール溶液を90%以上に濃縮し、結晶種を添加攪拌して箱型容器に分散し、数時間後にオパール様外観の固結塊を容器から取り出し、これらを積み重ねて長時間冷却と固結の内部充実を俟つて、粉砕又は切削した後、乾燥、篩別けを行つて製品とする。

②　造粒方式

ソルビトール濃縮液を比較的大量の結晶性ソルビトール粉末を流動させつつ、その上に噴射し、結晶性ソルビトール粉末の多粒子間間隙に、ソルビトール濃縮液を抱持せしめ、後者の固結を俟つて粉砕し、その一部を製品とし他を循環使用する。

上記の固化粉砕法①は、塊状体を多数貯蔵し、処理せざるを得ないために労働生産性が低く、工程が多段階から構成されているため、その管理も容易でない。更に固化ソルビット塊の粉砕に当り、塊内部に残存する溶液部分が、粉砕によつて被面に露出し、これが粉体のベトツキの原因となり、ケーキングを起し易く実用上あまりに欠点が大きい。

又上記造粒方式②は、粉体と液体を接触結合させて乾燥する機構に基いている。この造粒方式では液量を粉体量に対して増量するに従い、液滴粒によつて膠着捕集される粉体粒子量が増加し、しかもそれら凝集粒子の2次、3次等々の凝集が添加液量に応じて増大し、極限においては、粉体の装置内一塊化まで発展し、最早や作業不可能になるので比較的大量の粉体の存在下に比較的少量の液体を均等分散する必要がある。

ソルビトール等の糖アルコールの場合は、この

ような造粒方式で粉体化するためには、粉体上に噴霧する濃縮液は粉体量の1／3～1／4（乾物比）に止めなければならない。このことは装置内に2／3～3／4量の粉体が繰返し循環利用されていることを意味し、装置効率を1／3～1／4とするのみならず、製品の熱風接触平均時間を3～4倍にせざるを得ない。しかも造粒された粒子は常に必らず数倍の粒径に生長するから、これを粉砕機にかける必要がある。しかもこのようにして得られる粉末は顆粒状ではなく、大きな塊を粉砕した不定形の粒子に過ぎない。

一方顆粒状の粒子は、保存中に固化せず、溶解し易く、且つ連続的生産が可能なため労働生産性が高く、得られた製品を容器に機械的に連続充填が出来る流動性を有する利点があるが、上記の公知方法ではこのような顆粒状粉末を得ることが出来ない。尚、ぶどう糖においては、スプレードライ法により粉末化することが知られているが、（特公昭39－4834）ぶどう糖におけるスプレー乾燥法をそのまま結晶性糖アルコールの粉末化に適用することは出来ない。

それは、ぶどう糖は本来結晶し易い性質を有しているが、糖アルコールは結晶性を有するものであつても、その結晶性がはるかに小さく、ぶどう糖の粉末化法では粉末が得られないのである。

この様に特異な性質を有する糖アルコールを粉末化するために、本発明者等は研究の結果、特殊な手段を施こすことにより問題を解決し、本発明を完成したのである。

本発明においては、まず糖アルコール溶液の濃度が過飽和でなければいけないことはないが、この溶液に粉末状の糖アルコールを加えて、粉末の存在する状態で熟成しなければならない。そして乾燥手段として噴霧乾燥方式を用いる。

従つて、糖アルコール溶液の濃度が薄ければ、多くの糖アルコール粉末を加える必要があり、好ましくは糖アルコール溶液を予じめ濃縮し、出来れば過飽和にしておくことが良い結果を与える。

つぎに、粉末状の糖アルコールを加えた後の熟成は本発明の要点の一つであり、この熟成工程を経ずして噴霧乾燥は不可能である。すなわち、熟成中に溶液の粘度が低下し噴霧と顆粒形成を円滑にすることが出来る。この熟成中の粘度の低下現象は、糖アルコールに限つて見られる特殊な現象

であり、ぶどう糖においては逆に粘度が増大することから見て、全く予想できなかつた糖アルコール独自の特殊な性質である。

以上のように糖アルコールの粉末化とぶどう糖の粉末化が全く技術内容を異にするものであることが理解できる。

溶液の濃度、粉末の添加及び熟成は、総て糖アルコールの粉末化の際に共通して必要とされるが、粉末の吸着量、熟成時間並びに噴霧乾燥時の粘度は、糖アルコールの種類により多少の差異がある。

例えば、ソルビトールを使用した場合は、ソルビトール溶液中に25％～45％の粉末状のソルビトールが存在する状態で25℃～50℃で、15時間～24時間熟成すると、良好な結果を得る。又この熟成後の噴霧乾燥する際の粘度は20000～50000 cpsである。

この他例えば、キシリトールの場合は、キシリトール溶液中に20％～40％のキシリトール粉末が存在する状態で25℃～50℃で、15時間～24時間熟成すると、良好な結果を得る。又この熟成後の噴霧乾燥する際の粘度は、1000～5000 cpsである。

他の糖アルコールも大体同様である。

本発明を糖アルコールの代表的物質であるソルビトールを例にとり、具体的に説明する。

ソルビトールは、親水性、従つて吸湿性が極めて強く、温度26.7℃、相対湿度（R.H）80％において100gのソルビトールは、56gの水分を吸収して完全に溶液状態となり、又純ソルビトールの溶解度は、20℃で約70％、30℃で約74％と高い水溶性と緩やかな溶解度勾配を示す。

（他の糖アルコールもほぼ同様の性状を有する。）

このような溶解性状をもつソルビトールを、マスキット状に調整するためには、高度に濃縮した溶液から晶出作業を行う必要があるが、仮に80％以上の溶液に少量のシードを混入して放置すると、結晶粒子の成長が起る前に濃縮液全体のゲル化が起り、針状晶への移向は遅々として進まない。

この場合、例えばニーダー等の強力機械攪拌下に上記晶出作業を行うと溶液全体が固結して攪拌不能状態となる。

因みに、ソルビトールを始めとする結晶性糖アルコール溶液をそのまま噴霧乾燥すると、乾燥後

粒粉体が得られるが、このものは糖アルコール溶液が極限まで水分を喪失した、云わば固結溶液、即ち固溶体であつて結晶性を有せず顕微鏡下において、透明なガラス球に見えるが、これを外気中に露呈すれば、たちまちにして吸湿し、粉体間膠着によつて流動性を失い、やがて全体が一塊となり粉体的性質を失う。

この様に単に糖アルコール溶液を噴霧乾燥しても、安定した糖アルコール粉体は得られない。

その濃度が約８０％前後のソルビトール溶液に、比較的多量の結晶粉末を混和すると、ソルビトール溶液は全溶液のダル化を経過することなく、正常な熟成経過が見られその粘性が低下し、噴霧乾燥の容易なマヌキソトをソルビトール等の溶液についても調製でき、従つて、工業的に極めて有利な乾燥粉末化法である噴霧乾燥法を適用し得るに至つた。

ソルビトール、マヌキソトを噴霧乾燥するに際し、乾燥粒子中に包含されるソルビトール濃縮液が幾らかの遊離水分を残し、結晶成長し得る条件下にあることが理論的に望ましく、マヌの濃縮液が凝集結晶群の内部に収容されることが必要と考えられる。実験によれば、ソルビトールマヌキソト中の結晶量は少くとも２０％以上の結晶ソルビトールが存在すれば、作業は不可能ではないが、乾燥粉末を円滑且短時間に排出し、且安定した製品を得るためには、マヌキソト中３０％以上の結晶ソルビトールの存在することが望ましいことが判明した。

マヌキソト状ソルビトールの噴霧乾燥直後の形態は、マヌキソト中に含まれていた結晶群の凝集粒子にソルビトール濃縮液が包含された形になつており、温度に敏感に作用し、温風によつて粒子が軟化し、更に高温では全体が高粘度の流動塊となつてしまう。従つて乾燥機の排風温度は、ソルビトールの融点、軟化点等の熱的性質を考慮して選定されなければならない。

かくして得られる粒体は、顕微鏡下で観察すると、通常針状結晶の凝集した光沢に富む球状粒子群で、顆粒といわれている粉末である。

ソルビトールを例にとつて具体的に説明したが、他の糖アルコール例えばマンニトール、イノシトール、キシリトール等でも全く同様である。

この様なマヌキソト及び又はマヌキソト調整前

の溶液中に糖類、合成甘味料、天然甘味料、色素、医薬、有機酸、その他の水溶性物質を緊密に混合し、或は又香料、油脂、顔料、医薬品、その他の非水溶性物質を微粉状態で混合して、噴霧乾燥法等の手段で乾燥し、各乾燥微粉粒子中に均等に、それ等添加物を包含する結晶糖アルコールの顆粒状粉末等の製造も亦容易である。

但し、混和される他の物質は、本発明の実施に支障を来たさないものであり、且つ適切な添加量であり、得られる製品の耐湿安定性等の品位に対しても、悪影響を及ぼさないものであることが必要である。

従つて本発明は、結晶性糖アルコールと他の有用物質とから成る混合粉末の製法をも提供するものであることが理解され得よう。

以上の通り、本発明はソルビトールを始めとする高溶解性及び晶出特異性を有する結晶性糖アルコールの顆粒状粉末の製造に関し技術管理の容易にして高効率な工業生産の新規方法を提供し得たものであり、又得られる製品の品位は、それが主として糖アルコール結晶から構成せられ、極めて耐湿安定性に優れ、粉体流動性に富むなど顕著な進歩を達成し得たものである。

次に実施例について本発明を説明する。

実施例　1

７５％ソルビトール液５kgをジヤケツト付結晶機に仕込み、撹拌して温度を３０℃に保持するよう調製する。一方結晶粉体のソルビトール１.２５kgを上記溶液中に少しづつ加え、均等に分散させ撹拌を継続すると、凡そ3時間にしてクリーム状となるが、この段階での粘度はポンプ輸送出来ない程度に高い。更に撹拌を継続すると、結晶析出に伴う溶液側の濃度低下のため粘度が漸減し２０時間後に３０００cps／３０℃に下降した。

このようにして得たマヌキソト状ソルビトールを噴霧乾燥し、ソルビトール粉体を得た。送風温度６５℃で殆んど乾燥機内壁面での軟化膠着は見られなかつた。

乾燥粉末は単に放置するだけで、粒子内結晶が進み、粒子硬度と対湿安定性を増大する。尚低水分含量の製品を希望する場合には、ロータリードライヤー或は、流動層乾燥機などを用い熱風乾燥して短時間に、水分含量２％以下の製品が得られる。この段階でソルビトール粉末は、７０～８０

℃の乾燥熱風に耐える。

顕微鏡下で観察すると、透明な針状結晶群から成る顆粒状の光輝ある粉体であることが解る。

実施例 2

77%ソルビトール液5kgをジャケット付結晶機に仕込み、撹拌しつつ、温度30℃において、実施例1で得た結晶粉末ソルビトール0.75kgを上記溶液中に少しづつ加えて、クリーム状の均質コロイド状とし、撹拌を同温度で継続し、24時間後実施例1と同条件下で噴霧乾燥し、結晶性の顆粒状ソルビトール粉末を得た。

実施例 3

82%のソルビトール液5kgをジャケット付結晶機に仕込み撹拌しつつ、温度を45℃に保持するよう調整し、さきに得た結晶性顆粒状ソルビトール1kgを少しづつ加えて、均質なクリーム状コロイドとし、撹拌を45℃で継続して24時間後、マスキット状ソルビトールを得、実施例1、2と同様条件下で噴霧乾燥し、顆粒状ソルビトール粉末を得た。

実施例 4

実施例1の如く、75%キシリトール液5kgを結晶機で30℃で撹拌し、粉末キシリトール0.75kgを上記溶液中に少しづつ加えて、クリーム状の均質コロイド状とし、15時間同温度で撹拌し、3000 cps の粘度で上記同条件で噴霧乾燥し、結晶性顆粒状キシリトールを得た。検鏡外観は実施例1、2、3で得た製品に酷似しており、耐湿安定性粉体流動性など良好であつた。

実施例 5

実施例1の如く、75%ソルビトール液5kgを結晶機で30℃で撹拌し、これにステビオサイド粉末20gを少量の水で溶かして加え、緊密に混合し、これに結晶粉末ソルビトールを少しづつ添加して、均質なクリーム状とし、24時間30℃で撹拌、持続して、ステビオサイドを均等に溶存したマスキット状ソルビトールを得、これを実施例1の如く噴霧乾燥し、甘味が砂糖と同等のソルビトール結晶を主成分とする結晶性顆粒状の前記同様の粉体を得た。

比較例 1

実施例1と同様の条件で結晶粉末ソルビトールを添加することなく噴霧乾燥したが粉体は乾燥機内壁に堆積し排出不可能となつた。その一部を採つて検鏡すると無色透明の球状粒子であることが確認された。この粒子は外気中ガラス板上で吸湿固着した。

比較例 2

80%濃度のソルビトール溶液5kgに結晶粉末ソルビトール150gを加え30℃においてジャケット付結晶機中で撹拌し、マスキット調製を試みたが、30分後オパール色のゲル状態となり、次いで固結して長時日変化が見られなかつた。即ち粉末化し得なかつた。

EXHIBIT D

advantageous compared to spray-drying.

BY MR. MURPHY:

Q Sir, there are specific factual statements in the summaries of these paatents as set forth in your patent. I'm going to point out a specific sentence to you and ask you if you verified the accuracy of that statement. I'm looking at column 3, line 63.

INTERPRETER: May I translate that before you do that?

MR. MURPHY:

Q The sentence beginning moreover, "Moreover, the product always contains a very high content of fine particles, like the product described in Japanese Patent Application JP 61-85330."

Did you verify the accuracy of that statement before you --

A I did not verify that point.

Q If you look at column 4, line 6, it says, "A powder is thus obtained whose particle size is between 5 and 150 microns. It has been verified that the size of the particles according to this process is, just as with the JP 80-36646 and JP

61-85330 processes described above, always very low, so much so that the mean diameter of the particles is between 50 and 75 microns." Did you verify that statement in your patent?

A Personally I did not verify that point. Roquette must have verified it.

Q What's your basis for stating that Roquette must have verified it?

A The drafting of this document was written, drafted. I don't recall by which service, but -- and I was asked to verify the points that concerned me, that were related to me.

Q Who asked you to make that verification?

A After 15 years, I don't recall.

MR. MURPHY: I'm going to show the witness Defendant's Exhibit 22 and I'm going to ask him to refer to a specific page, and I have only a couple of questions related to that specific page.

(Defendant's Exhibit 22 was identified.)

BY MR. MURPHY:

Q You can set aside --

A Okay. Can we make a break, five minutes? Two minutes?

Q Let's review just this document.

EXHIBIT E

hooked up to the microphones.

(Plaintiff's counsel conferred briefly outside the room.)

BY MR. MURPHY:

Q In 1993 did you review the 146 patent?

A I don't recall.

Q Is it correct that the description of the 146 patent in your 77 patent characterizes the process for production of mannitol according to the 146 patent as a spray-drying process?

A Yes.

Q If you'd look at line 8 of column 4, starting actually at the end of line 7, there's a statement beginning or reading, "It has been verified that the size of the particles according to this process is, just as with the JP 80-36646 and JP 61-85330 processes described above, always very low, so much so that the mean diameter of the particles is between 50 and 75 microns."

INTERPRETER: And is there a question?

BY MR. MURPHY:

Q How did you verify that the mean diameter of the particles according to those patents was at the value between 50 and 75 microns?

A I don't recall.

MR. MURPHY: Let's take a five-minute break.

VIDEOGRAPHER: We're off the record. The time is approximately 10:25 p.m. -- I'm sorry, a.m.

(Recess)

VIDEOGRAPHER: We're back on the record. The time is approximately 10:35 a.m.

BY MR. MURPHY:

Q Mr. Serpelloni, did you instruct anyone to make that verification concerning the mean particle size for those patents identified here in column 4?

A I don't recall.

Q Did you ever see any documentation that records data to support that verification?

A I don't recall.

Q Do you understand that you submitted a declaration in this case affirming that you had reviewed your patent application and believed the statements to be true when you submitted it to the U.S. Patent Office; is that correct?

MR. RIGLER: When you said "in this case," you were not referring to this action?

Mr. Serpelloni hasn't submitted any declaration in

EXHIBIT F

INTERROGATORY NO. 6

Identify and describe in detail each effort, if any, by SPI to avoid infringement of any claim of the '777 Patent including any changes to the composition, properties or manufacturing process of a product imported into, sold, offered for sale or manufactured in the United States.

RESPONSE TO INTERROGATORY NO. 6

SPI Pharma objects to this contention interrogatory as premature because Roquette, the party bearing the burden of proof, has not yet set forth the factual or legal basis for any infringement contentions, nor has it indicated which claims it believes have been infringed by the Mannogem® EZ Spray Dried Mannitol product. SPI Pharma further objects to this contention interrogatory to the extent it seeks information protected from disclosure by the attorney-client privilege, work-product doctrine, or other applicable privilege.

Subject to and without waiving the foregoing general and specific objections, SPI Pharma responds that its investigations are ongoing, and it will supplement its response to this interrogatory as appropriate as information becomes available.

SPI Pharma further states that, pursuant to Fed. R. Civ. P. 33(d), the information requested by Roquette regarding the subject matter of this Interrogatory may be derived or ascertained from documents to be produced by SPI Pharma in due course in response to Roquette's First Set of Document Requests. Accordingly, in further response to this Interrogatory, SPI Pharma will produce responsive, non-privileged documents within its possession, custody or control.

INTERROGATORY NO. 7

State in detail each basis or fact upon which you will rely in support of SPI's second affirmative defense that the '777 Patent is invalid, specifying for each of the four listed sections of title 35 (§§ 101, 102, 103, and 112) the particular claims which are alleged to be invalid under each subsection and the detailed reasons supporting the allegation.

RESPONSE TO INTERROGATORY NO. 7

SPI Pharma objects to this contention interrogatory as premature because it calls for disclosure of expert opinion. SPI Pharma further objects to this interrogatory to the extent it seeks discovery of information that is protected from disclosure by the attorney-client privilege, work-product doctrine, or other applicable privilege.

Subject to and without waiving the foregoing general and specific objections, and reserving the right to supplement or change this response following further investigation and discovery, SPI Pharma responds that the claims of the '777 patent are invalid under 35 U.S.C. §§ 101, 102, 103, and 112. The claims are inoperable, anticipated, rendered obvious and/or indefinite, alone or in combination, by at least the following:

1. FR 2,571,045
2. EP-A-0,179,703
3. FR 2,571,046
4. EP-A-0,179,428
5. References cited on the face of the '777 patent and/or referred to during prosecution of the '777 patent

SPI Pharma further states that, pursuant to Fed. R. Civ. P. 33(d), the information requested by Roquette regarding the subject matter of this Interrogatory may be derived or ascertained from documents to be produced by SPI Pharma in response to Roquette's First Set of Document Requests, including without limitation the file history of the '777 patent and the foregoing publicly available documents. Accordingly, in further response to this Interrogatory, SPI Pharma will produce responsive, non-privileged documents within its possession, custody or control.